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| <p>(51) International Patent Classification ⁵ : C07D 239/78, A61K 31/505 C07D 239/84, 239/86, 239/94 C07D 401/14, 403/14, 413/14</p> | <p>A1</p> | <p>(11) International Publication Number: WO 93/13079 (43) International Publication Date: 8 July 1993 (08.07.93)</p> |
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| <p>(54) Title: ANTIFOLATE QUINAZOLINES</p> <p>(57) Abstract</p> <p>The present invention relates to certain quinazoline compounds capable of inhibiting folate metabolic pathways, to pharm- aceutical compositions containing these compounds, and to the use of these compounds to inhibit folate metabolic pathways, in- cluding all effects derived from the inhibition of folate metabolic pathways. Effects derived from the inhibition of folate metabo- lic pathways include the inhibition of the growth and proliferation of the cells of higher organisms and microorganisms, such as bacteria, yeasts and fungi. Such effects may include the inhibition of the enzymes thymidylate synthase or dihydrofolate reduc- tase, or both. A process for preparing the quinazoline antifolate compounds according to the present invention is also disclosed.</p> | | |

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Description

ANTIFOLATE QUINAZOLINES

Technical Field

The present invention relates to certain quinazoline compounds which are capable of inhibiting folate metabolic pathways, to pharmaceutical compositions containing these compounds, and to the use of these compounds to inhibit folate metabolic pathways, including all effects derived from the inhibition of folate metabolic pathways. Effects derived from the inhibition of folate metabolic pathways include the inhibition of the growth and proliferation of the cells of higher organisms and microorganisms, such as bacteria, yeasts and fungi. Such effects may include the inhibition of the enzymes thymidylate synthase or dihydrofolate reductase, or both. A process for preparing the antifolate quinazoline compounds according to the present invention is also disclosed.

Background Art

A large class of antiproliferative agents includes antimetabolite compounds. A particular subclass of antimetabolites known as antifolates or antifols are antagonists of the vitamin folic acid. Typically, antifolates closely resemble the structure of folic acid and incorporate the characteristic p-benzoyl glutamate moiety of folic acid. Because the glutamate moiety of folic acid takes on a double negative charge at physiological pH, this compound and its analogues cannot passively diffuse into a cell and must have an active, energy-driven transport system to cross the cell membrane and exert a metabolic effect.

The earliest antifolates were aminopterin and methotrexate ("MTX"). MTX has been used widely in the treatment of human neoplastic diseases, such as malignant diseases. The cytotoxic action of MTX is ascribed generally to its inhibition of the enzyme dihydrofolate reductase ("DHFR"), a key enzyme which maintains the pools of one-carbon carrying tetrahydrofolates. One of the known causes

of resistance to MTX, which has the glutamate moiety characteristically found in folic acid analogues, is reduced transport across the cell membrane.

Two more recent inhibitors of DHFR, piritrexim and trimetrexate, both of which lack the glutamate moiety, also have been developed. These two agents penetrate the cell wall by passive diffusion and, thus, can affect both normal tumor cells and those resistant because of a transport defect. These compounds have been found active even against tumor cells having an MTX transport defect. Because they are more soluble than MTX in organic solvents and in lipids, they have been termed lipophilic DHFR inhibitors. Additionally, trimetrexate may be active against opportunistic infections which occur in patients infected with HIV (human immunodeficiency virus, AIDS).

Another valid target for an antifolate is the enzyme thymidylate synthase ("TS"). TS catalyzes the C-methylation of 2'-deoxyuridylate ("dUMP") to provide 2'-deoxythymidylate ("dTMP"). This one-carbon transfer reaction is critical to cell division. Thus, a number of folate analogues have been synthesized and studied for their ability to inhibit TS. A prototypic, specific, tight-binding inhibitor of TS, 10-propargyl-5,8-dideazafolic acid (T. R. Jones et al., "A Potent Antitumor Quinazoline Inhibitor of Thymidylate Synthetase: Synthesis, Biological Properties and Therapeutic Results in Mice," Eur. J. Cancer 17:11 (1981)), has shown activity against ovarian, liver and breast cancer, with, however, troublesome hepatic and renal toxicities (A. H. Calvert et al, "A Phase I Evaluation of the Quinazoline Antifolate Thymidylate Synthase Inhibitor, N10-Propargyl-5,8-Dideazafolic Acid, CB3717," J. Clin. Oncol. 4:1245 (1986)). By addressing two properties in this class of molecule (solubility and capability for intracellular polyglutamation), a superior second generation analogue (ICI D1694) was developed.

As with DHFR, lipophilic TS inhibitors also have been developed recently (E. M. Berman et al., "Substituted

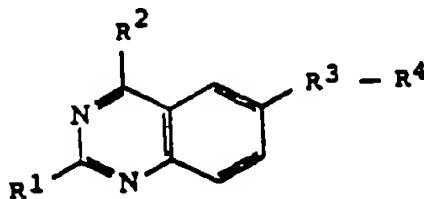
Quinazolinones as Anticancer Agents," U.S. Patent No. 4,857,530; T.R. Jones et al., "Antiproliferative Cyclic Compounds," Copending U.S. Patent Application No. 07/432,338 filed September 30, 1988; M.D. Varney et al., "Antiproliferative Substituted Naphthalene Compounds," U.S. Patent Application No. 07/583,970 filed September 17, 1990; S.H. Reich et al., "Antiproliferative Substituted Tricyclic Compounds," U.S. Patent Application No. 07/587,666 filed September 25, 1990; and L.R. Hughes et al., "Anti-tumour Agents," European Patent Application No. 373891, filed December 12, 1989).

Disclosure of the Invention

The present invention relates to novel quinazoline compounds which are capable of inhibiting folate metabolic pathways, to pharmaceutical compositions containing these compounds, and to the use of these compounds to inhibit folate metabolic pathways, including all effects derived from the inhibition of folate metabolic pathways. Effects derived from the inhibition of folate metabolic pathways include the inhibition of the growth and proliferation of the cells of higher organisms and of microorganisms, such as bacteria, yeasts and fungi. Such effects may include the inhibition of the enzymes thymidylate synthase or dihydrofolate reductase, or both.

Best Mode for Carrying Out the Invention

The present invention relates to quinazoline compounds having the formula I



I

wherein:

R¹ and R², which may be the same or different, represent electron-donating substituents;

R^3 represents a $-S-CH_2-$ group, a $-CH_2-S-$ group or a $-N(R^5)-CH_2-$ group, wherein R^5 is hydrogen or a lower alkyl; and

R^4 represents a substituted or unsubstituted aryl or heteroaryl group;

provided that, when R^1 and R^2 both represent $-NH_2$, R^4 does not represent (a) an unsubstituted phenyl; (b) an unsubstituted naphthyl; (c) a substituted phenyl selected from the group consisting of mono-, di- or tri-(lower alkyl)phenyl, mono- or di- halophenyl, hydroxyphenyl, mono-, di- or tri-(lower alkoxy)phenyl, carboxyphenyl, carb-(lower alkoxy)phenyl, nitrophenyl, aminophenyl, mono- or di-(lower alkyl) aminophenyl, and acetamidophenyl; (d) a phenyl substituted in the para-position with any of the following groups: $-CO-NHR_b$ where R_b is such that NH_2-R_b is an amino acid, a poly(amino acid), a lower alkyl ester of an amino acid, or a lower alkyl ester of a poly(amino acid); (e) a substituted naphthyl selected from the group consisting of halonaphthyl, hydroxynaphthyl, nitronaphthyl, aminonaphthyl and lower alkoxy naphthyl; or (f) an unsubstituted furyl, thienyl or pyridyl group.

As used herein, the language "capable of inhibiting folate metabolic pathways" refers to the ability of a compound to diffuse across a cell membrane and block the action of tetrahydrofolic acid-dependent reactions. By doing so, such a compound may effectively inhibit the growth and proliferation of the cells of higher organisms and microorganisms, such as bacteria, yeasts and fungi. Of particular interest, is that certain quinazoline compounds according to the present invention are either capable of inhibiting the enzyme thymidylate synthase or capable of inhibiting the enzyme dihydrofolate reductase, or both.

The language "capable of inhibiting the enzyme thymidylate synthase," or the like, refers to a compound having a TS inhibition constant K_i of less than or equal to about $10^{-4}M$. The compounds according to the present invention preferably have TS K_i values in the range of less

than about 10^{-5} M, preferably less than about 10^{-6} M, more preferably less than about 10^{-9} M and most preferably less than about 10^{-12} M.

The language "capable of inhibiting the enzyme dihydrofolate reductase," or the like, refers to a compound having a DHFR inhibition constant K_i of less than or equal to about 10^{-6} M. The compounds according to the present invention preferably have DHFR K_i values in the range of less than about 10^{-8} M, preferably less than about 10^{-10} M, more preferably less than about 10^{-12} M and most preferably less than about 10^{-13} M.

Typical substituents for the electron-donating substituents R^1 and R^2 of formula I above include $-\text{NH}_2$, $-\text{NH}$ - (lower alkyl), $-\text{NHOH}$, $-\text{NHNH}_2$, $-\text{S}$ -(lower alkyl) and $-\text{NR}_6\text{R}_7$, wherein R_6 and R_7 represent substituted or unsubstituted lower alkyl groups. As used herein, the language "lower alkyl", "lower alkoxy" and the like refers to groups having one to six carbon atoms. For example, "lower alkyl" may refer to methyl, ethyl, n-propyl, isopropyl and the like. Preferably, at least one of R^1 and R^2 is $-\text{NH}_2$. More preferably, both R^1 and R^2 are $-\text{NH}_2$.

As indicated above, substituent R^3 of formula I may be a $-\text{S}-\text{CH}_2-$ group, a $-\text{CH}_2-\text{S}-$ group or a $-\text{N}(\text{R}^5)-\text{CH}_2-$ group, wherein R^5 is hydrogen or a lower alkyl. Preferably, R^3 is a $-\text{N}(\text{R}^5)-\text{CH}_2-$ group. When R^3 is a $-\text{N}(\text{R}^5)-\text{CH}_2-$ group, R^5 is preferably a methyl or ethyl group.

The R^4 substituent of formula I can be any one of a large number of ring compounds selected from the group consisting of substituted or unsubstituted aryl and heteroaryl rings. Examples of useful aryl ring groups include phenyl, 1,2,3,4-tetrahydro-naphthyl, naphthyl, phenanthryl, anthryl and the like. Examples of typical heteroaryl rings include 5-membered monocyclic ring groups such as thienyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl and the like; 6-membered monocyclic groups such as pyridyl, pyranal, pyrazinyl, pyrimidinyl, pyridazinyl and the like; and

polycyclic heterocyclic ring groups such as benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalaziny, naphthyridiny, quinoxaliny, quinazoliny, cinnoliny, pteridiny, 4H-carbazolyl, carbazolyl, beta-carboliny, phenanthridiny, acridiny, perimidiny, phenanthroliny, phenaziny, isothiazolyl, phenothiaziny, phenoxaziny and the like.

However, when R^1 and R^2 both represent $-NH_2$, R^4 does not represent (a) an unsubstituted phenyl; (b) an unsubstituted naphthyl; (c) a substituted phenyl selected from the group consisting of mono-, di- or tri-(lower alkyl)phenyl, mono- or di- halophenyl, hydroxyphenyl, mono-, di- or tri-(lower alkoxy)phenyl, carboxyphenyl, carb-(lower alkoxy)phenyl, nitrophenyl, aminophenyl, mono- or di-(lower alkyl) aminophenyl, and acetamidophenyl; (d) a phenyl substituted in the para-position with any of the following groups: $-CO-NHR_b$ where R_b is such that NH_2-R_b is an amino acid, a poly(amino acid), a lower alkyl ester of an amino acid, or a lower alkyl ester of a poly(amino acid); (e) a substituted naphthyl selected from the group consisting of halonaphthyl, hydroxynaphthyl, nitronaphthyl, aminonaphthyl and lower alkoxy naphthyl; or (f) an unsubstituted furyl, thienyl or pyridyl group.

Notwithstanding the foregoing exceptions for when both R^1 and R^2 are $-NH_2$, R^4 is preferably a monocyclic or bicyclic aryl or heteroaryl ring. More preferably, R^4 is a phenyl, naphthyl or monocyclic or bicyclic heteroaryl ring, and most preferably, R^4 is phenyl.

As discussed previously, R^4 may be unsubstituted, or R^4 may be substituted with one or more of a wide variety of electron-donating and electron-withdrawing substituents. As used herein, the language "electron-withdrawing" refers to groups such as $-NO_2$, $-CN$, carboxy, halogen, SO_2R^8 , wherein R^8 is as defined hereunder, and the like. The language

"electron-donating" refers to groups such as $-NH_2$, $-NH$ -(lower alkyl), $-NHOH$, $-NHNH_2$, $-S$ -(lower alkyl) and $-NR_6R_7$, wherein R_6 and R_7 represent lower alkyl groups, and the like.

In most cases, the use of an electron-withdrawing substituent on R^4 of formula I results in both TS and DHFR inhibition. In contrast, only DHFR inhibition has been noticeably achieved in the absence of an electron-withdrawing substituent. Even so, TS and DHFR inhibition are merely exemplary of the antifolate activity of the quinazoline compounds of the present invention. Indeed, certain compounds may demonstrate an antifolate activity besides TS or DHFR inhibition, or even demonstrate an antifolate activity in addition to TS and DHFR inhibition. For example, the quinazoline compounds according to the claimed invention may demonstrate activity against serine hydroxymethyltransferase, glycineamino ribotide transformylase and aminoimidazolecarboxamide ribotide transformylase. Further, certain compounds may show antiproliferative activity stemming from a completely different locus of action than the inhibition of folic metabolic pathways, for example, by intercalation into nucleic acid.

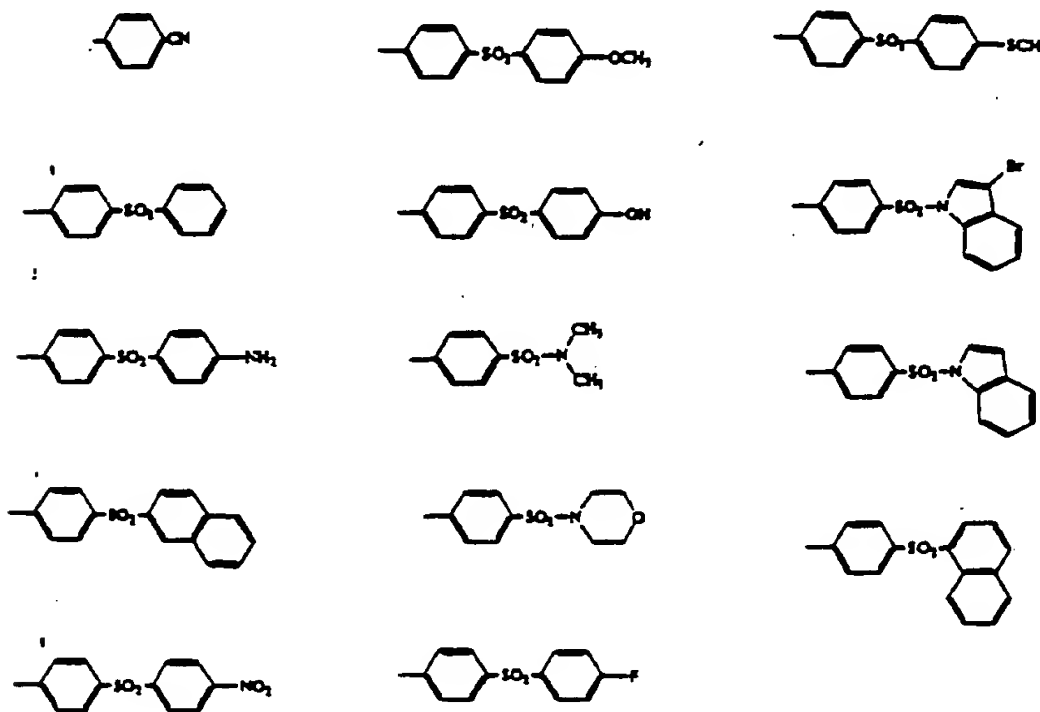
Typical substituents for R^4 include halogen, hydroxy, lower alkoxy, lower alkyl, hydroxyalkyl, fluoroalkyl, amino, (lower alkyl)-amino, $-CN$, $-NO_2$, carbalkoxy, carbamyl, carbonyl, carboxy, amino acid carbonyl, amino acid sulfonyl, sulfamyl, sulfanilyl, sulfhydryl, sulfino, sulfinyl, sulfo, sulfonamido, sulfonyl, (lower alkyl)-thio, substituted or unsubstituted phenylsulfonyl, phenylmercapto, phosphazo, phosphinico, phosphino, phospho, phosphono, phosphoro, phosphoroso, mercaptoaryl, and the like.

In a preferred embodiment, R^4 is substituted with at least one electron-withdrawing group such as $-NO_2$, $-CN$, carboxy, halogen, $-SO_2R^8$, wherein R^8 is as defined hereunder, and the like. More preferably, R^4 is substituted with a $-CN$ or $-SO_2$ group. Even more preferably, R^4 is substituted by a $-SO_2R^8$ group, wherein R^8 represents an aryl or heteroaryl group, such as phenyl, naphthyl, indole, or morpholino. Most

preferably, R^4 is substituted in the para-position (i.e., the 4-position) by a $-\text{SO}_2-\text{R}^8$ group, wherein R^8 is a phenyl group.

When R^4 is a phenyl group substituted by a $-\text{SO}_2-\text{R}^8$ group wherein R^8 is an aryl or heteroaryl group, R^8 may also be substituted with a variety of substituents, such as those discussed above for R^4 . Preferably, R^8 is phenyl substituted by hydroxy, lower alkoxy, amino, (lower alkyl)-amino, (lower alkyl)-thio, nitro, carboxy, halogen and the like.

Particularly preferred structures for R^4 include:



A preferred class of compounds according to the present invention includes those compounds according to formula I, wherein at least one of R^1 and R^2 is $-\text{NH}_2$, R^3 is $-\text{N}(\text{lower alkyl})\text{CH}_2-$, preferably $-\text{N}(\text{CH}_3)\text{CH}_2-$ and R^4 is phenyl substituted at the para position by $-\text{SO}_2-\text{R}^8$, wherein R^8 is an aryl or heteroaryl group as discussed above. More preferably, R^8 is unsubstituted phenyl or phenyl substituted

by hydroxy, lower alkoxy, amino, (lower alkyl)-amino, (lower alkyl)-thio, nitro, carboxy, halogen and the like.

A particularly preferred class of compounds according to the present invention includes those compounds according to formula I, wherein both R^1 and R^2 are $-NH_2$, R^3 is $-N(CH_3)CH_2-$ or $-N(CH_2CH_3)CH_2-$, and R^4 is phenyl substituted at the para position by $-SO_2-R^8$, wherein R^8 is an aryl or heteroaryl group as discussed above. More preferably, R^8 is unsubstituted phenyl or phenyl substituted by hydroxy, lower alkoxy, amino, (lower alkyl)-amino, (lower alkyl)-thio, nitro, carboxy, halogen and the like.

Another preferred class of compounds according to the present invention includes those compounds according to formula I, wherein at least one of R^1 and R^2 is $-NH_2$, R^3 is $-S-CH_2-$ or $-CH_2-S-$, and R^4 is phenyl substituted at the para position by $-SO_2-R^8$, wherein R^8 is an aryl or heteroaryl group as discussed above. More preferably, R^8 is unsubstituted phenyl or phenyl substituted by hydroxy, lower alkoxy, amino, (lower alkyl)-amino, (lower alkyl)-thio, nitro, carboxy, halogen and the like. Most preferably, both R^1 and R^2 are $-NH_2$.

Another preferred class of compounds according to the present invention includes those compounds according to formula I, wherein at least one of R^1 and R^2 is $-NH_2$, R^3 is $-N(CH_3)CH_2-$, and R^4 is a cyanophenyl group. More preferably, both R^1 and R^2 are $-NH_2$.

Particularly preferred compounds according to the present invention include:

- 2,4-Diamino-6-(N-(4-cyanobenzyl)amino)quinazoline;
- 2,4-Diamino-6-(N-(4-cyanobenzyl)methylamino)quinazoline;
- 2-Amino-4-(methylthio)-6-(N-(4-cyanobenzyl)methylamino)quinazoline;
- 2-Amino-4-(methylamino)-6-(N-(4-cyanobenzyl)methylamino)quinazoline;
- 2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline;

2-Amino-4-(hydroxyamino)-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline;
2-Amino-4-hydrazino-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((4-nitrophenyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((4-aminophenyl)sulfonyl)
benzyl)methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((4-hydroxyphenyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-(N,N-
dimethylsulfamoyl)benzyl)methylamino)
quinazoline;
2,4-Diamino-6-(N-(4-(morpholinosulfonyl)benzyl)methylamino)
quinazoline;
2,4-Diamino-6-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((4-(methylthio)phenyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((3-bromo-1-indolyl)sulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-((1-indolyl)sulfonyl)benzyl)methylamino)
quinazoline;
2,4-Diamino-6-(N-(4-((1-naphthyl)sulfonyl)benzyl)methylamino)
quinazoline;
2,4-Diamino-6-(N-(4-(2-naphthyl)sulfonyl)benzyl)methylamino)
quinazoline;
4-Amino-2-methylthio-6-(N-(4-
(phenylsulfonyl)benzyl)methylamino)
quinazoline;
2,4-Bis(hydrazino)-6-(N-(4-
(phenylsulfonyl)benzyl)methylamino)
quinazoline;

2,4-Bis(methylamino)-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline;
4-Amino-2-(methylamino)-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline;
2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)ethylamino)
quinazoline;
2,4-Diamino-6-((4-phenylsulfonyl)phenylthiomethyl)
quinazoline;
2,4-Diamino-6-((4-phenylsulfonyl)benzylthio)quinazoline;
2,4-Diamino-6-(N-((4-pyridyl)methyl)methylamino)quinazoline;
and
2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)
quinazoline glucuronate.

Another aspect of the present invention relates to processes of making the antifolate quinazoline compounds of formula I.

A preferred process according to the present invention for making the antifolate quinazoline compounds of formula I, wherein R^1 - R^4 have the same meanings as described previously, comprises the steps of:

- (1) reacting a compound $L - CH_2 - R^4$ with a (lower alkyl)-amine, wherein L is a leaving group, for example, a halogen atom such as Br, Cl, F and I, and R^4 has the same meaning as described above for formula I;
- (2) reacting the product of step (1) with 5-chloro-2-nitrobenzonitrile to form a nitro-containing intermediate;
- (3) reducing the nitro group of the intermediate of step (2); and
- (4) reacting the product of step (3) with a cyclization reagent.

The first step of reacting the compound $L - CH_2 - R^4$ with a (lower alkyl)-amine compound can be carried out under widely varying conditions, but is preferably carried out with an excess of the amine, and if not, then in the presence of a base, typically at a temperature varying from about 0°C to about 100°C, preferably from about room temperature to about 60°C, and most preferably at about room temperature.

Step (2) may also be carried out under widely varying conditions, but is typically carried out in a solvent, preferably DMSO, and in the presence of a base, such as CaCO_3 , at a temperature varying from about room temperature to about 189°C , preferably from about 60°C to about 150°C , and most preferably from about 80°C to about 120°C .

Step (3), the reducing step, can be performed under widely varying reduction conditions, but is preferably carried out in an organic solvent such as ethanol, methanol, ethyl acetate, tetrahydrofuran or acetic acid, in the presence of a reducing agent such as a KBH_4/CuCl or hydrogen gas, under a vapor pressure of one atmosphere or higher, and at a temperature varying from about room temperature to about 100°C , preferably from about room temperature to about 60°C , and most preferably at about room temperature. Further, a reduction catalyst such as Raney nickel, palladium on charcoal, palladium on barium sulfate and the like may also be used where appropriate.

In step (4), cyclization of the product of step (3) may be induced by reacting the product of step (3) with a cyclization reagent such as chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide, thiourea, and the like. If thiourea is used as the cyclization reagent, compounds according to the present invention may be obtained by further reacting the product of step (4) with NaH , followed by iodomethane. Step (4) may be carried out under widely varying conditions, but is typically carried out in the presence of an acid at a temperature varying from about room temperature to about 200°C , preferably from about room temperature to about 180°C , and most preferably from about 150°C to about 165°C .

Another process of making the antifolate quinazoline compounds of formula I, wherein $\text{R}^1\text{-R}^4$ have the same meanings as discussed previously, comprises the steps of:

(1) reacting a compound $\text{L} - \text{CH}_2 - \text{R}^4$ with a 2-amino-5-(lower alkyl amino)benzonitrile, wherein L is a leaving

group, for example, a halogen atom such as Br, Cl, F and I, the lower alkyl amino is, for example, methylamino, ethylamino and the like, and R^4 has the same meaning as described above for formula I; and

(2) reacting the product of step (1) with a cyclization reagent.

The first step of reacting the compound $L - CH_2 - R^4$ with a 2-amino-5-(lower alkyl amino)benzonitrile compound can be carried out under widely varying conditions, but is typically carried out in the presence of a base at a temperature varying from about room temperature to about 150°C, preferably from about 45°C to about 110°C, and most preferably at about 60°C.

In step (2), the cyclization step, the reagent used to induce cyclization may be a wide variety of compounds such as chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide, thiourea, and the like. If thiourea is used, compounds according to the present invention may be obtained by further reacting the product of step (2) with NaH, followed by iodomethane. Step (2) may be carried out under widely varying conditions, but is typically carried out in the presence of an acid at a temperature varying from about room temperature to about 200°C, preferably from about room temperature to about 180°C, and most preferably from about 150 to about 165°C.

Another process according to the present invention for making the compounds of formula I, wherein $R^1 - R^4$ have the same meaning as discussed previously, comprises the steps of:

(1) reacting a compound $HS - R^4$ with a 5-(L-(lower alkyl)-2-((trifluoroacetyl)amino)benzonitrile, wherein L is a leaving group, for example, a halogen atom such as Br, Cl, F and I, and R^4 has the same meaning as discussed above for formula I;

(2) lysing the trifluoroacetyl group of the product of step (1); and

(3) reacting the product of step (2) with a cyclization reagent.

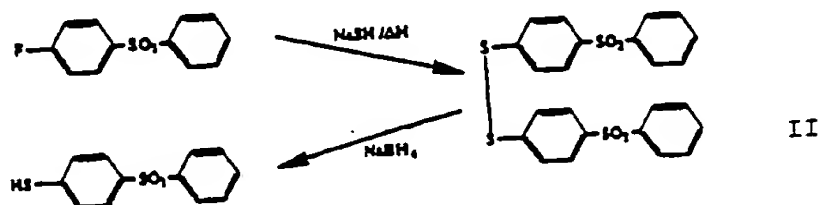
Step (1) can be carried out under widely varying conditions, but is typically carried out in the presence of a base at a temperature varying from about 0°C to about 100°C, preferably from about room temperature to about 60°C, and most preferably at about room temperature.

Step (2), which is a deprotection step, can be performed under widely varying lytic conditions, but is preferably carried out with methanolic ammonia at a temperature varying from about 0°C to about 100°C, preferably from about room temperature to about 60°C, and most preferably at about room temperature. As used herein, the language "lytic conditions" includes, but is not limited to, hydrolytic, alcoholic, ammonolytic and aminolytic conditions.

In step (3), the cyclization step, the reagent used to induce cyclization may be a wide variety of compounds such as chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide, thiourea, and the like. If thiourea is used, compounds according to the present invention may be obtained by further reacting the product of step (3) with NaH, followed by iodomethane.

Step (4) may be carried out under widely varying conditions, but is typically carried out in the presence of an acid at a temperature varying from about room temperature to about 200°C, preferably from about room temperature to about 180°C, and most preferably from about 150°C to about 165°C.

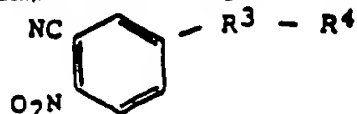
A preferred method of forming the HS - R⁴ compound of step (1) is carried out according to the following reaction scheme:



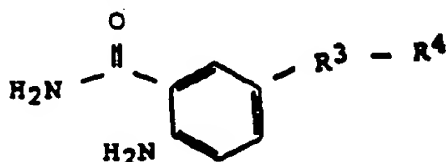
This reaction may be carried out under widely varying conditions, but is typically carried out at a temperature varying from about room temperature to about 150°C, preferably from about 60°C to about 120°C, and most preferably at about 90°C.

Another process according to the present invention for making the compounds of formula I, wherein R^3 is $S-CH_2$ or CH_2-S , and R^4 has the same meaning as discussed previously, comprises the steps of:

- (1) reacting a compound having the formula

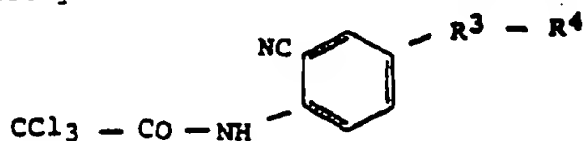


wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$, with a reducing agent to give a compound having the formula



wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$;

- (2) reacting the product of step (1) with trichloroacetyl chloride to give a compound having the formula



wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$;

- (3) lysing the trichloroacetyl group of the product of step (2); and
 (4) reacting the product of step (3) with a cyclization reagent.

The first step of reducing the nitro group with concomitant hydrolysis of the nitrile group may be carried out under widely varying conditions which employ a reducing agent, but is preferably carried out (i) with stannous chloride dihydrate in ethyl acetate or in ethanol at a

temperature varying from about 0°C to about 77°C, preferably from about room temperature to about 77°C, and most preferably at 70°C; (ii) with a combination of stannous chloride dihydrate and sodium borohydride in ethanol at a temperature varying from about 0°C to about 78°C, preferably from about room temperature to about 78°C, and most preferably at 60°C; (iii) with triiron dodecacarbonyl in a mixture of methanol and benzene at a temperature varying from about room temperature to about 80°C, preferably from about 40°C to about 80°C, and most preferably at 80°C; or (iv) with hydrazine hydrate combined with graphite in ethanol at a temperature varying from about 0°C to about 78°C, preferably from about room temperature to about 78°C, and most preferably at about 78°C.

Step (2) may also be carried out under widely varying conditions, but is typically carried out with an excess of the reagent in the presence of a base in an inert solvent at a temperature varying from about 0°C to about 100°C, preferably from about room temperature to about 60°C, and most preferably at about room temperature.

Step (3), which is a deprotection step, can be performed under widely varying lytic conditions, but is preferably carried out with methanolic ammonia at a temperature varying from about 0°C to about 100°C, preferably from about room temperature to about 60°C, and most preferably at about room temperature.

In step (4), the cyclization step, the reagent used to induce cyclization may be a wide variety of compounds such as chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide, thiourea, and the like. If thiourea is used, compounds according to the present invention may be obtained by further reacting the product of step (4) with NaH, followed by iodomethane.

It should be noted that, in many cases, it may be necessary to provide protecting groups either before, after

or during the course of preparing the compounds according to the present invention.

A suitable protecting group for a ring nitrogen, such as may be included in a heteroaryl group, is for example, a pivaloyloxymethyl group, which may be removed by hydrolysis with a base such as sodium hydroxide; a tert-butyloxycarbonyl group, which may be removed by hydrolysis with an acid, such as hydrochloric acid or trifluoroacetic acid, or with a base such as tetra-n-butylammonium fluoride ("TBAF") or lithium hydroxide; or a 2-(trimethylsilyl)ethoxymethyl group, which may be removed by TBAF or with an acid such as hydrochloric acid.

A suitable protecting group for a hydroxyl group is, for example, an esterifying group such as an acetyl or benzoyl group, which may be removed by hydrolysis with a base such as sodium hydroxide. Alternatively, when other groups present in the starting material do not contain an alkenyl or alkynyl group, the protecting group may be, for example, an alpha-arylalkyl group such as a benzyl group, which may be removed by hydrogenation in the presence of a catalyst such as palladium on charcoal or Raney nickel. An additional protecting group for a hydroxyl group is a group such as t-butyldiphenylsilyl (-Si-t-Bu-Ph₂), which may be removed by treatment with TBAF.

A suitable protecting group for a mercapto group is, for example, an esterifying group such as an acetyl group, which may be removed by hydrolysis with a base such as sodium hydroxide.

A suitable protecting group for an amino group may be, for example, an alkylcarbonyl group such as an acetyl group (CH₃CO-), which may be removed by treatment with an aqueous inorganic acid such as nitric, sulfuric or hydrochloric acid. Another protecting group for an amino group is an alkoxy carbonyl group such as a methoxycarbonyl or a tert-butyloxycarbonyl group. These groups may be removed by treatment with an organic acid such as trifluoroacetic acid.

A suitable protecting group for a primary amino group is, for example, an acetyl group, which may be removed by treatment with an aqueous inorganic acid such as nitric, sulfuric, or hydrochloric acid, or a phthaloyl group, which may be removed by treatment with an alkylamine such as dimethylaminopropylamine or with hydrazine.

A suitable protecting group for a carboxy group may be an esterifying group, for example, a methyl or an ethyl group, which may be removed by hydrolysis with a base such as sodium hydroxide. Another useful protecting group is a tert-butyl group, which may be removed by treatment with an organic acid such as trifluoro-acetic acid.

Preferred protecting groups include an esterifying group, an alpha-arylalkyl group, an alkylcarboxyl group, a substituted or unsubstituted alkoxy carbonyl group, a phthaloyl group, a pivaloyloxymethyl group, a methyl oxyether-type group such as methoxymethyl or 2-(trimethylsilyl)ethoxymethyl, or a silicon group such as a tert-butyldiphenylsilyl group.

The antifolate quinazoline compounds of the present invention, which may be employed in the pharmaceutical compositions according to the present invention, include all of those compounds described above, as well as pharmaceutically acceptable salts of these compounds. Pharmaceutically acceptable acid addition salts of the compounds of the invention containing a basic group are formed, where appropriate, with strong or moderately strong organic or inorganic acids in the presence of a basic amine by methods known in the art. Exemplary of the acid addition salts which are included in this invention are maleate, fumarate, lactate, oxalate, ethanesulfonate, ethanesulfonate, benzenesulfonate, tartrate, glucuronate citrate, sulfate, phosphate and nitrate salts. Pharmaceutically acceptable base addition salts of compounds of the invention containing an acidic group are prepared by known methods from organic and inorganic bases, and include nontoxic alkali metal and alkaline earth bases, for example, calcium, sodium and

potassium hydroxides; ammonium hydroxides; and nontoxic organic bases such as triethylamine, butylamine, piperazine and tri(hydroxymethyl)-methylamine.

As stated above, the compounds of the invention possess antiproliferative activity, a property which may express itself in the form of antitumor activity. A compound of the invention may be active per se or it may be a pro-drug that is converted in vivo to an active compound. Preferred compounds of the invention are active in inhibiting the growth of the L1210 cell line, a mouse leukemia cell line which can be grown in tissue culture. Such compounds of the invention are also active in inhibiting the growth of bacteria such as Escherichia coli gram negative bacteria which can be grown in culture. The compounds of the invention may also be active inhibiting the growth of bacteria.

The antifolate compounds according to the present invention, as well as the pharmaceutically acceptable salts thereof, may be incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutically acceptable carriers may be employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline and water.

Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g. solution), such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving steps such as mixing, granulating and compressing, when necessary for tablet forms; or mixing, filling and dissolving

the ingredients, as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural and rectal administration.

The composition of the invention may further comprise one or more other compounds which are antitumor agents, such as a mitotic inhibitors (e.g., vinblastine), alkylating agents (e.g., cis-platin, carboplatin and cyclophosphamide), other DHFR inhibitors (e.g., methotrexate, piritrexim and trimetrexate), other TS inhibitors, antimetabolites (e.g., 5-fluorouracil and cytosine arabinoside), intercalating antibiotics (e.g., adriamycin and bleomycin), enzymes (e.g., asparaginase), topoisomerase inhibitors (e.g., etoposide) or biological response modifiers (e.g., interferon).

The composition of the invention may also comprise one or more other compounds, including antibacterial, antifungal, antiparasitic, antiviral, antipsoriatic and anticoccidial agents. Exemplary antibacterial agents include, for example, sulfonamide such as sulfamethoxazole, sulfadiazine, sulfameter or sulfadoxine; DHFR inhibitors such as trimethoprim, bromodiazepim or trimetrexate; penicillins; cephalosporins; aminoglycosides; bacteriostatic inhibitors of protein synthesis; the quinolonecarboxylic acids and their fused isothiazolo analogs.

Another aspect of the invention relates to a therapeutic process of inhibiting the folate metabolic pathways, which process comprises administering to a host, such as a vertebrate host, for example, a mammal or bird, an amount effective to inhibit the folate metabolic pathways of a compound according to the present invention. The compounds of the invention are particularly useful in the treatment of mammalian hosts, such as human hosts, and in the treatment of avian hosts.

Any of the antifolate compounds described above, or pharmaceutically acceptable salts thereof, may be employed in the therapeutic process of the invention. The compounds of the invention may be administered in the form of a

pharmaceutically acceptable composition comprising a diluent or carrier, such as those described above. Doses of the compounds preferably include pharmaceutical dosage units comprising an efficacious quantity of active compound. By an efficacious quantity is meant a quantity sufficient to inhibit the folate metabolic pathways and derive the beneficial effects therefrom through administration of one or more of the pharmaceutical dosage units. An exemplary daily dosage unit for a vertebrate host comprises an amount of up to about 1 gram of active compound per kilogram of the host, preferably one half of a gram, more preferably 100 milligrams, and most preferably about 50 milligrams per kilogram of the host.

The selected dose may be administered to a warmblooded animal or mammal, for example a human patient, in need of treatment mediated by folate metabolic pathways inhibition by any known method of administration, including topically (e.g. as an ointment or cream), orally, rectally (e.g., as a suppository), parentally, by injection or continuously by infusion, intravaginally, intranasally, intrabronchially, intraaurally or intraocularly.

The antifolate compounds according to the present invention may be further characterized as producing any one or more of an antiproliferative effect, an antibacterial effect, an antiparasitic effect, an antiviral effect, an antipsoriatic effect, an antiprotozoal effect, an anticoccidial effect or an antifungal effect. The compounds are especially useful in producing an antitumor effect in a vertebrate host harboring a tumor.

EXAMPLES

The structure of all compounds of the invention were confirmed by proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis and, in certain cases, by mass spectroscopy.

Proton magnetic resonance spectra were determined using a General Electric QE-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dq, doublet of quartets; t, triplet; br s, broad singlet; br d, broad doublet; br m, broad multiplet; br, broad signal; m, multiplet. EI mass spectra were determined using a VG 7070E-HF high resolution mass spectrometer using the direct insertion method, an ionizing voltage of 70 eV, and an ion source temperature of 200°C. Desorption chemical ionization (DCI) spectra were also determined on this spectrometer, using ammonia as the reagent gas. FAB mass spectra were determined using a VG ZAB or a VG 70SE spectrometer. Infrared absorption spectra were taken on a Perkin-Elmer 457 or on a Midac M2000 spectrometer. Elemental microanalysis gave results for the elements stated within $\pm 0.4\%$ of the theoretical values.

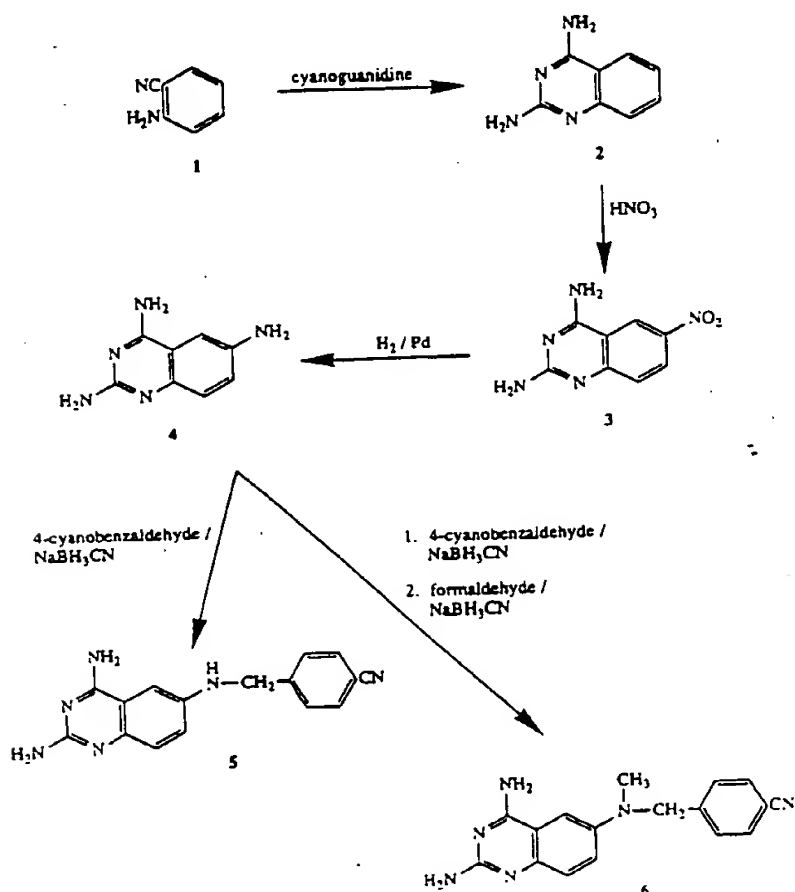
General Procedures

N,N-Dimethylformamide (DMF) was dried over activated (250°C) 3-Å molecular sieves; N,N-dimethylacetamide (DMA, Aldrich Gold Label grade), and hexamethylphosphoramide (HMPA, Aldrich) were similarly dried. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. AIBN is 2,2'-azobis(2-methylpropionitrile). Diglyme is bis(2-methoxyethyl) ether. Ether refers to diethyl ether. Petrol refers to petroleum ether of bp 36-53°C. Flash chromatography was performed using Silica gel 60 (Merck Art 9385). Where the crude solid (x g) was insoluble in the chosen eluant, it was dissolved in a more polar solvent, and Merck Art 7734 (gravity) silica (4x g) added. The slurry was

evaporated to dryness on a rotary evaporator fitted with a coarse glass frit to prevent spraying of the silica. The coarse glass frit was then applied to the column. Thin layer chromatographs (TLC) were performed on precoated sheets of silica 60F₂₅₄ (Merck Art 5719). For chromatography on alumina, TLC plates were aluminium oxide 60F₂₅₄ (Merck Art 5731), and flash column packing was basic alumina (Merck Art 1076). Extracts were dried over Na₂SO₄ or MgSO₄. Melting points were determined on a Mel-Temp apparatus and are corrected.

Example 1: Preparation of Compounds 5 and 6

Compounds 5 and 6 were prepared according to the following reaction scheme:



Preparation of Compound (2) --

2,4-Diaminoquinazoline

2,4-Diaminoquinazoline (2) was prepared from anthranilonitrile (1) by a published method [J. Davoll and A.M. Johnson, *J. Chem. Soc., Section C*, 997, (1970)] conducted on the same scale (0.4 mol). The yield was 36.7 g (57%) of a product suitable for further use.

Preparation of Compound (3) --

2,4-Diamino-6-nitroquinazoline

2,4-Diamino-6-nitroquinazoline (3) was prepared from 2,4-diaminoquinazoline by a published method (*ibid*, method a) conducted on a 0.19 mol scale. Yield >90%.

Preparation of Compound (4) --

2,4,6-Triaminoquinazoline

2,4,6-Triaminoquinazoline (4) was prepared by a slightly modified procedure of the above reference. A suspension of 2,4-diamino-6-nitroquinazoline (25 g) in DMF (900 mL) containing 10% Pd:C (5 g) was stirred for 22 h at 25°C and atmospheric pressure. The mixture was filtered through celite, and the filtrate was evaporated under reduced pressure to give a solid which was collected on a filter with the aid of Et₂O. Recrystallization from H₂O (2 L) afforded the product (4.98 g). A second crop (5.82 g) was also obtained to give a total yield of 51%.

Preparation of Compound (5) --

2,4-Diamino-6-(N-(4-cyanobenzyl)amino)quinazoline

4-Cyanobenzaldehyde (0.433 g, 3.3 mmol, 1.1 eq) was added to a solution of 2,4,6-triaminoquinazoline (0.525 g, 3 mmol) and NaBH₃CN (0.207 g, 3.3 mmol, 1.1 eq) in EtOH (50 mL). 0.1 N NaCl was then added until pH 6. The reaction was stirred for 3 days at 25°C and then acidified to pH 2 to quench any remaining borohydride. The mixture was brought to pH 8 with satd. NaHCO₃ and partitioned between half-satd. brine (200 mL) and CH₂Cl₂ (50 mL). The organic layer was dried and concentrated to give an oily residue (0.425 g) which was redissolved in EtOH (30 mL), treated with NaBH₃CN (0.8 g) and briefly warmed to convert remaining Schiff base

evident by TLC. The resulting light yellow solution was acidified to pH 2 with 1N HCl, and then brought to pH 8 with NaHCO₃, added to brine (100 mL), and extracted with CH₂Cl₂ (50 mL) and EtOAc (100 mL). The combined organic layers were dried and concentrated to give a pale yellow oil (269 mg) which was chromatographed on SiO₂ (200 g) using 4.5% Et₃N, 18% MeOH, 77.5% CH₂Cl₂ as eluant to give the pure product as a yellow-orange (30 mg, 14%), mp 265°C dec. NMR (Me₂SO-d₆) δ 4.41 (d, 2H, J = 6.3 Hz, CH₂), 5.94 (s, 2H, NH₂), 6.29 (t, 1H, J = 6.3 Hz, NH), 6.95-7.07 (m, 3H, H⁵, H⁷, H⁸), 7.27 (s, 2H, NH₂), 7.58 (d, 2H, J = 8.2 Hz, aromatic), 7.75 (d, 2H, J = 8.2 Hz, aromatic). Anal. (C₁₆H₁₄N₆ · 0.12 Et₃N · 0.5 H₂O) C, H, N; the Et₃N was seen in the NMR spectrum. HRMS (C₁₆H₁₄N₆)⁺ calcd, 290.1280; found, 290.1284.

Preparation of Compound (6) --

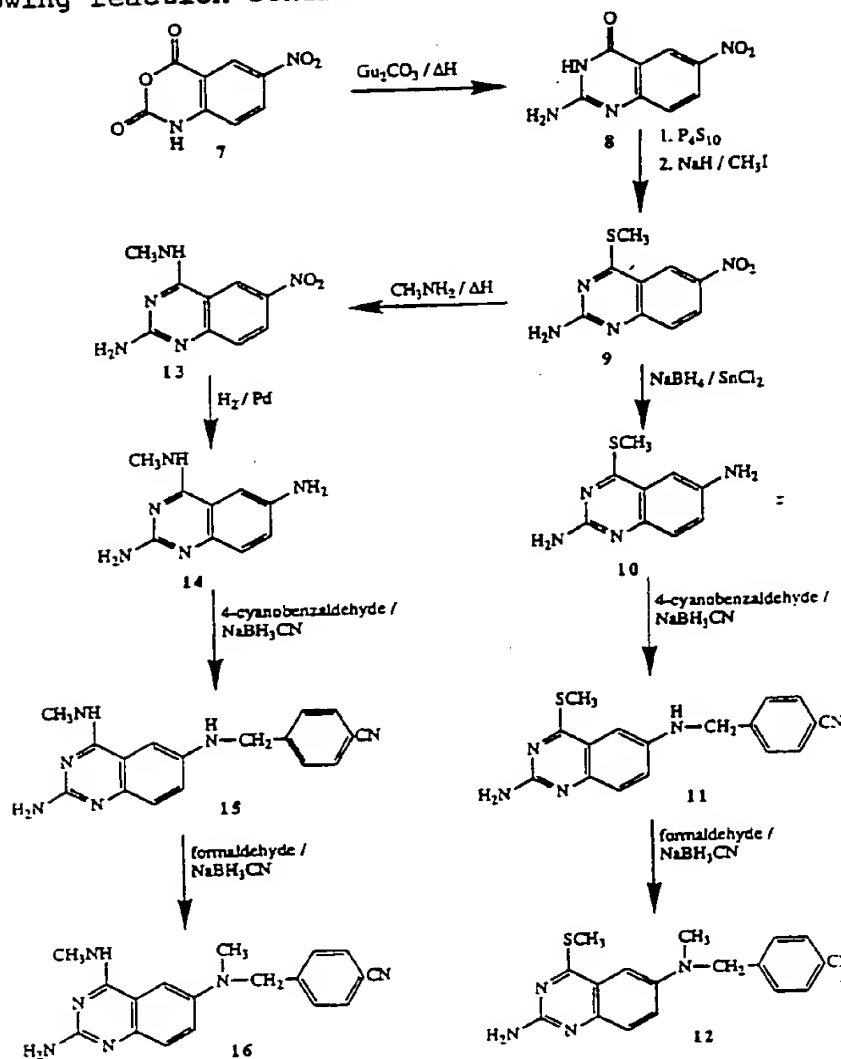
2,4-Diamino-6-(N-(4-cyanobenzyl)methylamino)quinazoline

A mixture of 2,4,6-triaminoquinazoline (1.0 g, 5.7 mmol) in EtOH (130 mL) was briefly heated to give an amber solution which was acidified, with formation of a precipitate, to pH 6.9 with 1 N HCl. 4-Cyanobenzaldehyde (0.822 g, 6.3 mmol, 1.1 eq) was added in one portion followed by NaBH₃CN (0.71 g, 11.4 mmol, 2 eq). The pH was maintained between 6 and 7 by periodic addition of 1 N HCl. After 50 min., 37% HCHO_{aq} (2.1 mL, 28.5 mmol, 5 eq) and additional NaBH₃CN (0.36 g, 1 eq) were added. The mixture was stirred for 13 h, during the first 8 h of which the pH was maintained between 6.2 and 6.9. The reaction was quenched with 1N HCl to pH 1.4 causing the turbid yellow mixture to clarify. The solution was brought to pH 8 with satd. NaHCO₃, and the resulting yellow solid was collected, washed with H₂O, and dried in a desiccator. The crude mass (1.1 g) was dissolved in MeOH and coated onto silica (5 g) and flash chromatographed on SiO₂ (100 g) using 5% Et₃N, 20% MeOH, 75% CH₂Cl₂ as eluant to give a reaction by-product 2,4-diamino-6-(N,N-dimethyl)aminoquinazoline (438 mg) plus the pure desired product as a yellow solid (64 mg, 3.7%), mp 258°C dec. NMR (Me₂SO-d₆) δ 2.97 (s, 3H, CH₃), 4.65 (s, 2H, CH₂), 5.89 (s, 2H, NH₂), 7.14-7.22 (m, 3H,

H^5, H^7, H^8), 7.32 (s, 2H, NH_2), 7.40 (d, 2H, $J = 8.3$ Hz, aromatic), 7.78 (d, 2H, $J = 8.2$ Hz, aromatic). Anal. ($C_{17}H_{16}N_6 \cdot 0.3 H_2O$) C, H, N. HRMS ($C_{17}H_{16}N_6$)⁺ calcd, 304.1436; found, 304.1426.

Example 2: Preparation of Compounds 12 and 16

Compounds 12 and 16 were prepared according to the following reaction scheme:



Preparation of Compound (8) --

2-Amino-4-hydroxy-6-nitroquinazoline

2-Amino-4-hydroxy-6-nitroquinazoline (8) was prepared from 5-nitroisatoic anhydride (7) by a published method [J.B.

Hynes, Y.C.S. Yang, J.G. McGill, S.J. Harmon and W.L. Washtien, *J. Med. Chem.*, 27, 232 (1984)] conducted on twice the scale to give a rust-colored solid (82%) suitable for further use.

Preparation of Compound (9) --

2-Amino-4-(Methylthio)-6-nitroquinazoline

A suspension of 2-amino-4-hydroxy-6-nitroquinazoline (85%, 24.25 g, 100 mmol) and P_4S_{10} (71.12 g, 160 mmol) in CH_3CN (24 mL) was mechanically stirred under argon and ice cooled. Et_3N (83.6 mL, 600 mmol, 6 eq) was added in two portions during 3 min to give dark brown solution which was heated at 50°C for 91 h. 1N NaOH (500 mL) was added to the reaction mixture to give pH 9, and the mixture was then cooled to below 20°C in ice and CH_3I (29.9 mL, 480 mmol, 4.8 eq) added in one portion. The heterogeneous, gummy reaction mixture was stirred vigorously; after 15 min, TLC (SiO_2 /EtOAc) showed incomplete conversion of the intermediate thione to product, and thus 6N NaOH (100 mL) and CH_3I (30 mL) were added and the mixture was stirred in ice for a further 1 h. H_2O (400 mL) was added to the mixture, and the liquid supernatant was decanted from the brown gum. The gum was dissolved in glacial HOAc (200 mL) to give a solution which was then brought to pH 6 with 1N NaOH. The resulting crude solid was filtered off, washed with water and redissolved in boiling HOAc (800 mL). The solution was charcoal treated and brought to pH 5 with 2N NaOH. The resulting yellow-orange, flocculent solid was filtered off, washed with water, and dried in a desiccator (12.41 g, 51%). An analytical sample was recrystallized from toluene/hexane as a yellow solid, mp 281-283°C, NMR (Me_2SO-d_6) δ 2.66 (s, 3H, CH_3), 7.44 (d, 1H, $J = 9.3$ Hz, H^8), 7.58 (s, 2H, NH_2), 8.34 (dd, 1H, $J = 9.3$, 2.6 Hz, H^7), 8.58 (d, 1H, $J = 2.6$ Hz, H^5), Anal. ($C_9H_8N_4O_2S$) C, H, N, S.

Preparation of Compound (10) --

2,6-Diamino-4-(methylthio)quinazoline

According to the method of T. Sato et al. [*Chem. Pharm. Bull.* 29, 1443, (1981)], a solution of 2-amino-4-(methylthio)-6-nitroquinazoline (3.08 g, 13 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (14.66 g, 65 mmol, 5 eq) in EtOH (300 mL) was heated at 60°C. A solution of NaBH_4 (0.25 g, 6.5 mmol, 0.5 eq) in EtOH (75 mL) was added during 5 min. The mixture was stirred for 10 min, basified to pH 8 with 1N NaOH, and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried and concentrated to give a crude orange-colored residue (2.3 g) which was coated onto silica (11.5 g) and flash chromatographed on SiO_2 (200 g) using CH_3CN as the eluant to give the pure product as a yellow solid (0.63 g, 23%) mp 209.5-211.5°C dec. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.56 (s, 3H, S- CH_3), 5.28 (s, 2H, NH_2), 6.19 (s, 2H, NH_2), 6.82 (d, 1H, $J = 2.4$ Hz, H^5), 7.08 (dd, 1H, $J = 8.9, 2.4$ Hz, H^7), 7.18 (d, 1H, $J = 8.9$ Hz, H^8). Anal. ($\text{C}_9\text{H}_{10}\text{N}_4\text{S}$) C, H, N, S.

Preparation of Compound (11) --

2-Amino-4-(methylthio)-6-

(N-(4-cyanobenzyl)amino)quinazoline

A solution of 2,6-diamino-4-(methylthio)quinazoline (0.6 g, 2.9 mmol) and 4-cyanobenzaldehyde (0.42 g, 3.2 mmol, 1.1 eq) in MeOH (75 mL) was adjusted to 6.3 with 0.1 N HCl. Solid NaBH_3CN (0.36 g, 5.8 mmol, 2 eq) was added, and the mixture was stirred at 25°C keeping the pH between 6 and 7 by periodic addition of 0.1 N HCl. At 2 h 45 min, further aldehyde (0.076 g, 0.2 eq) and NaBH_3CN (0.10 g, 0.55 eq) were added, followed at 4 h 40 min with yet further aldehyde (0.380 g, 1.0 eq). After 36 h, excessive hydride was quenched by the addition of 0.1 N HCl to pH 1, followed by basification to pH 8 with 1N NaOH. The solution was evaporated under reduced pressure to small volume and partitioned between brine (400 mL) and n-BuOH (2 x 50 mL). The combined organic layers were dried, and their content coated onto SiO_2 (5 g) by evaporation under reduced pressure. Flash chromatography on SiO_2 (100 g) with CH_3CN as the eluant.

gave the pure product as a yellow solid (460 mg, 49%) mp 228-229°C. NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory. Anal. ($\text{C}_{17}\text{H}_{15}\text{N}_5\text{S}$) C, H, N, S.

Preparation of Compound (12) --

2-Amino-4-(methylthio)-6-(N-(4-cyanobenzyl)methylamino)quinazoline

A mixture of 2-amino-4-(methylthio)-6-(N-(4-cyanobenzyl)quinazoline (0.44 g, 1.37 mmol), NaBH_3CN (0.17 g, 2.7 mmol, 2 eq), 37% HCHO_{aq} (0.51 mL, 6.85 mmol, 5 eq) and MeOH (125 mL) was stirred at 25°C for 46 h keeping the pH between 6 and 7 by the occasional addition of 0.1 N HCl. At 28 h, extra HCHO_{aq} (0.4 mL, 4 eq) was added. Excessive hydride was destroyed with 1N HCl to pH 1, followed by neutralization with 1 N NaOH. The mixture was poured into brine (1 L) and extracted with n-BuOH (2 x 125 mL). The extracts were dried, and their content coated onto silica (2.5 g). Flash chromatography on SiO_2 (50 g) using CH_3CN as eluant gave an analytically pure product as a yellow-orange solid (63 mg, 14%) mp 217-219°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.56 (s, 3H, S- CH_3), 3.07 (s, 3H, N- CH_3), 4.71 (s, 2H, CH_2), 6.34 (s, 2H, NH_2), 6.70 (d, 1H, $J = 2.7$ Hz, H^5), 7.28 (d, 1H, $J = 9.2$ Hz, H^8), 7.37 (dd, 1H, $J = 9.2, 2.7$ Hz, H^7), 7.42 (d, 2H, $J = 8.3$ Hz, aromatic), 7.79 (d, 2H, $J = 8.3$ Hz, aromatic). Anal. ($\text{C}_{18}\text{H}_{17}\text{N}_5\text{S}$) C, H, N, S. HRMS ($\text{C}_{18}\text{H}_{17}\text{N}_5\text{S}$)⁺ calcd, 335.1205; found, 335.1218.

Preparation of Compound (13) --

2-Amino-4-(methylamino)-6-nitroquinazoline

Anhydrous CH_3NH_2 (2.00 mL, 45 mmol, 7.9 eq) was added to a solution of 2-amino-4-(methylthio)-6-nitroquinazoline (1.34 g, 5.7 mmol) in DMF (80 mL) contained in a pressure tube. The resulting solution was heated at 70-100°C for 2 h 15 min, cooled to room temperature, carbon treated, and filtered. The filtrate was added slowly to H_2O (600 mL) to give a fine suspension of orange-colored solid product which was filtered, washed well with H_2O , and dried over P_2O_5 in vacuo (0.68 g, 54%) mp >300°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.96 (d, 3H, $J = 4.5$ Hz, CH_3), 6.88 (s, 2H, NH_2), 7.22 (d, 1H, $J = 9.3$ Hz,

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H⁸), 8.20 (dd, 1H, J = 9.3, 2.5 Hz, H⁷), 8.54 (d, 1H, J = 4.5 Hz, NH), 9.02 (d, 1H, J = 2.5 Hz, H⁵). Anal. (C₉H₉N₅O₂) C, H, N.

Preparation of Compound (14) --

2,6-Diamino-4-(methylamino)quinazoline

A suspension of 2-amino-4-(methylamino)-6-nitroquinazoline (0.67 g, 3.9 mmol), 10% Pd:C catalyst (0.33 g) in DMF (25 mL) was hydrogenated at 25°C and atmospheric pressure for 18 h after which additional catalyst (0.1 g) was added. The mixture was hydrogenated for 2 h more, then filtered. The solutes were coated onto silica (3 g) by evaporation and flash chromatographed on SiO₂ (60 g) using 5% Et₃N, 15% MeOH, 80% CH₂Cl₂ as the eluant. Evaporation of the appropriate fractions gave the desired product as a dark solid (0.195 g, 33%), mp 135-137°C. NMR (Me₂SO-d₆) δ 3.01 (d, 3H, CH₃), 5.43 (s, 2H, NH₂), 7.08-7.22 (m, 3H, H⁵, H⁷, H⁸), 7.59 (s, 2H, NH₂), 9.15 (d, 1H, J = 4.4 Hz, NH). This compound did not microanalyse well. HRMS (C₉H₁₁N₅)⁺ calcd, 189.1014; found, 189.1016.

Preparation of Compound (15) --

2-Amino-4-(methylamino)-6-

(N-(4-cyanobenzyl)amino)quinazoline

A solution of 2,6-diamino-4-(methylamino)quinazoline (0.619 g, 3.3 mmol), 4-cyanobenzaldehyde (0.98 g, 7.5 mmol, 2.3 eq), and NaBH₃CN (0.411 g, 6.6 mmol, 2 eq) in MeOH (100 mL) was stirred at 25°C for 1 h keeping the pH between 6 and 7. The mixture was brought to pH 1 to quench any excessive hydride and then neutralized to pH 7 with 1 N NaOH. The MeOH was evaporated, H₂O (300 mL) added, and the resulting mixture kept at 2°C for 3 days. A floating scum was removed with a spatula before the flocculent solid which had formed was collected, washed with H₂O, dried, (0.251 g) dissolved in nBuOH and coated onto gravity silica (1g). The scum was dissolved in n-BuOH, and the solution was dried (Na₂SO₄), treated with charcoal and filtered through celite. The filtrate was coated onto silica (4 g). Both batches of coated silica were combined and flash chromatographed on SiO₂

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(100 g) using 5% Et₃N, 15% MeOH, 80% CH₂Cl₂ as eluant. Appropriate fractions were evaporated to give the pure product as a yellow solid (273 mg, 24%), mp 263°C dec, NMR (Me₂SO-d₆) satisfactory. Anal (C₁₇H₆N₆ · 0.17 Et₃N · 1.9 H₂O) C,H,N; the Et₃N was seen in the NMR spectrum.

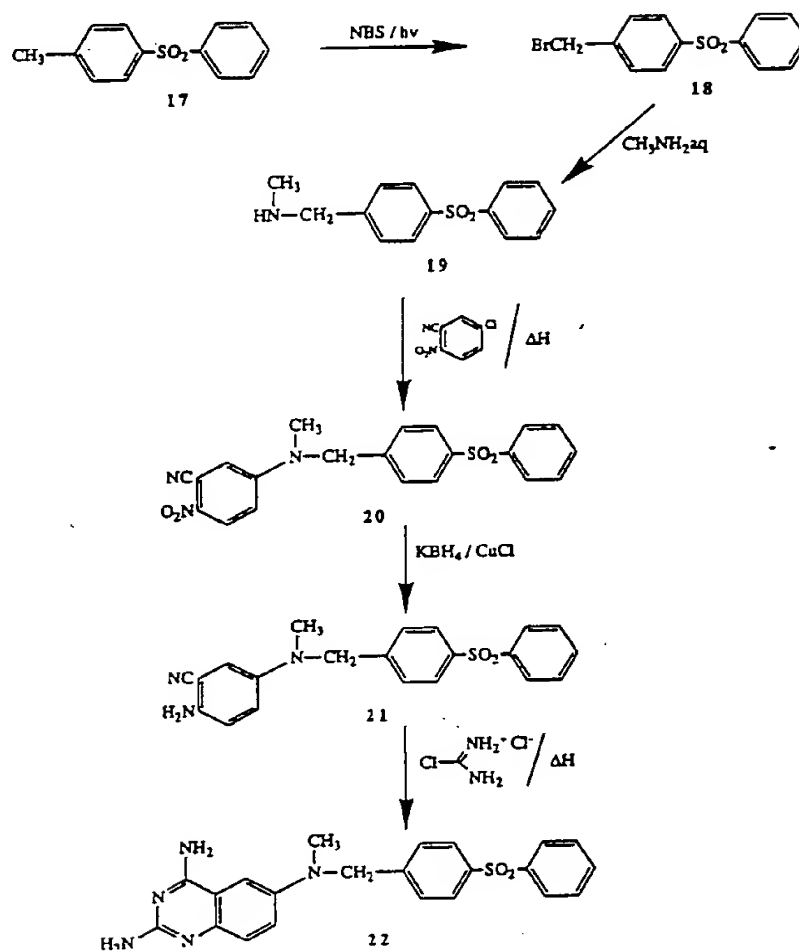
Preparation of Compound (16) --

2-Amino-4-(methylamino)-6-(N-(4-cyanobenzyl)methylamino)quinazoline

A solution of 2-amino-4-(methylamino)-6-(N-(4-cyanobenzyl)amino)quinazoline (0.207 g, 0.68 mmol), NaBH₃CN (0.086 g, 1.4 mmol, 2 eq) and 37% HCHO_{aq} (0.25 mL, 3.4 mmol, 5 eq) in MeOH (75 mL) was stirred at 25°C, and its pH kept between 6 and 7 by the occasional addition of 0.1 N HCl. Both at 19 h and at 49 h, further HCHO_{aq} (0.15 mL, 3 eq) and NaBH₃CN (0.042 g, 1 eq) were added. At 72 h, the excessive hydride was quenched with 0.1 N HCl, the mixture neutralized with 1 N NaOH, evaporated to dryness, dissolved in n-BuOH (50 mL), and coated onto silica (1g) by evaporation. Chromatography on SiO₂ (25 g) using 5% Et₃N, 10% MeOH, 85% CH₂Cl₂ as eluant afforded a technical quality product (62 mg, 29%). This material was coated onto silica (0.5 g) from MeOH and rechromatographed as above on SiO₂ (10 g) to give the pure product as a yellow solid (26 mg, 12% overall), mp 211.5-213.5°C. NMR (Me₂SO-d₆) δ 2.91 (d, 3H, J = 4.1 Hz, CH₃), 2.95 (s, 3H, CH₃), 4.66 (s, 2H, CH₂), 5.77 (s, 2H, NH₂), 7.08-7.19 (m, 3H, H⁵, H⁷, H⁸), 7.40 (d, 2H, J = 8.2 Hz, aromatic), 7.72 (d, 1H, J = 4.1 Hz, NH), 7.78 (d, 2H, J = 8.2 Hz, aromatic). Anal. (C₁₈H₁₈N₆) C,H,N. HRMS (C₁₈H₁₈N₆)⁺ calcd, 318.1593; found, 318.1578.

Example 3: Preparation of Compound 22

Compound 22 was prepared according to the following reaction scheme:

**Preparation of Compound (18) --****4-(Phenylsulfonyl)benzyl bromide**

A mixture of phenyl p-tolyl sulfone (17, 116.15 g, 0.5 mol) in CCl_4 (1.2 L) was heated to reflux to give an amber solution to which N-bromosuccinimide (94.34 g, 0.53 mol, 1.06 eq) was added. The refluxing mixture was irradiated for 45 min with a 200 watt bulb. The mixture was cooled and diluted

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with CH_2Cl_2 (1 L). The resultant solution was washed with warm H_2O (3 x 750 mL), dried, and evaporated to give the crude product as an off-white solid (158 g). From the integrals of the ^1H NMR signals of the side chains this material comprised 60% desired monobromide, 30% unreacted starter, and 10% dibromide. It was used without further purification.

Preparation of Compound (19) --

N-Methyl-4-(phenylsulfonyl)benzylamine

To a vigorously stirred mixture of a 40% w/w aqueous solution of methylamine (400 mL, 4.65 mol) and THF (200 mL) was added a solution of the above crude 4-(phenylsulfonyl)benzyl bromide (18, 158 g, ~0.3 mol) in THF (1 L) during 90 min at 25°C. The resulting solution was stirred for 1 h, then poured into a mixture of ice (500 g) and conc HCl (400 mL). The layers were separated, and the organic phase was concentrated *in vacuo*. The residue thus obtained was partitioned between 2N HCl (600 mL) and CH_2Cl_2 (500 mL). The acidic aqueous layers were combined, made alkaline to pH 13 with 6N NaOH (800 mL), and extracted with CH_2Cl_2 (3 x 1L), and the extracts were combined, dried, and concentrated *in vacuo* to give the product as a pale yellow solid (68.03 g, 52% overall from the tolyl sulfone). An analytical sample was prepared by flash chromatography on SiO_2 using 3% Et_3N in CH_3CN followed by recrystallization from $\text{EtOH}/\text{H}_2\text{O}$, mp 113.5-114.5°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.22 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 7.54-7.68 (m, 5H, aromatic), 7.88-7.96 (m, 4H, aromatic), NH not visible. Anal. ($\text{C}_{14}\text{H}_{15}\text{NO}_2\text{S}$) C, H, N, S.

Preparation of Compound (20) --

5-(N-(4-(phenylsulfonyl)benzyl)methylamino)-2-nitrobenzonitrile

A mixture of N-methyl-4-(phenylsulfonyl)benzylamine (29.44 g, 0.11 mol), 5-chloro-2-nitrobenzonitrile (20.45 g, 0.11 mol) and CaCO_3 (16.70 g, 0.165 mol, 1.5 eq) in DMSO (600 mL) was stirred at 110°C for 10 h. The yellow mixture was filtered through celite and the filtrate was divided into

halves. Each half was worked up by pouring into H₂O (2 L) plus brine (1 L) and extracting with EtOAc (2 x 500 mL). During the extraction, a solid formed at the interface which, following removal of the brine, was separated from the extracts by decantation, collected on a filter, and washed with H₂O then Et₂O, and dried. The combined EtOAc layers were dried and evaporated to give a solid product which was washed out of the evaporation flask onto a filter funnel with Et₂O and dried in a desiccator. The combined solids constituted the yellow crystalline product (20.08 g, 44%). The analytical sample was prepared by flash chromatography (SiO₂/EtOAc), mp 212.5-214.5°C. NMR (CDCl₃) δ 3.23 (s, 3H, CH₃), 4.73 (s, 2H, CH₂), 6.79 (dd, 1H, J = 9.5, 2.9 Hz, H⁴), 6.96 (d, 1H, J = 2.9 Hz, H⁶) 7.28-7.59 (m, 5H, aromatic), 7.94 (m, 4H aromatic), 8.18 (d, 1H, J = 9.5 Hz, H³). Anal. (C₂₁H₁₇N₃O₄S) C, H, N, S.

Preparation of Compound (21) --

2-Amino-5-(N-(4-(phenylsulfonyl)benzyl)
methylamino)benzonitrile

To a solution of 5-(N-(4-(phenylsulfonyl)benzyl)methylamino) 2-nitrobenzonitrile (28.27 g, 69 mmol) in CH₂Cl₂ (1300 mL) was added MeOH (1300 mL) and CuCl (20.6 g, 208 mmol, 3 eq). KBH₄ (26.06 g, 0.48 mol, 7 eq) was added during 15 min, and the mixture was then stirred for 50 min at 25°C. The black copper salts which had formed were filtered off and washed with CH₂Cl₂ (300 mL) and discarded. The organic phase was worked up in halves: each half was poured into H₂O (2 L), and extracted with CH₂Cl₂ (500 mL). The combined organic layers were washed with brine (500 mL), dried, and evaporated. The resulting dark brown residue was coated onto SiO₂ (75 g) from EtOAc and flash chromatographed on SiO₂ (500 g) using 30% hexane in EtOAc as eluant to give the purified product as a sticky yellow solid (13.73 g, 52.7%), mp 40°C. NMR (Me₂SO-d₆) δ 2.80 (s, 3H, CH₃), 4.46 (s, 2H, CH₂), 5.33 (s, 2H, NH₂), 6.68-6.71 (m, 2H, H³ & H⁶), 6.92 (dd, 1H, J = 9.1, 2.8 Hz, H⁴), 7.40 (d, 2H, J = 8.2 Hz, aromatic), 7.58-

7.68 (m, 3H, aromatic), 7.88-7.95 (m, 4H, aromatic). Anal. ($C_{21}H_{19}N_3O_2S$) C, H, N, S.

Preparation of Compound (22) --

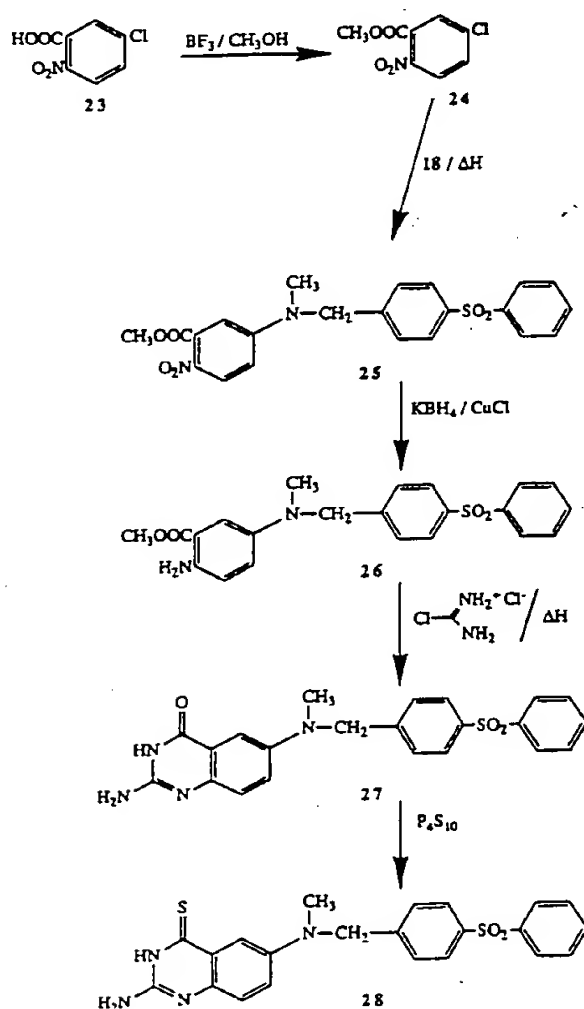
2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline

To a solution of 2-amino-5-(N-(4-phenylsulfonyl)-benzyl)methylamino)benzonitrile (13.73 g, 36 mmol) in diglyme (65 mL) was added chlorformamidine hydrochloride (5.02 g, 44 mmol, 1.2 eq), and the resulting slurry was heated at 150°C for 1 h 15 min. The mixture was cooled to 25°C, Et_2O (150 mL) was added and the resulting liquid layer was decanted from a brown resin. The liquid layer, when brought to pH 9 with NH_4OH , contained no desired product by TLC (SiO_2 /5% Et_3N , 10% MeOH, 85% CH_2Cl_2), and was thus discarded. The resin was treated with a mixture of DMF (100 mL), and Et_3N (13 mL, 88 mmol) and gently warmed to give a dark brown solution which was treated with charcoal and filtered. The charcoal was rinsed with MeOH (30 mL), and the combined filtrate was cooled. It was then poured onto ice (500 g) containing 1 N NaOH (100 mL) with stirring. The resulting crude orange-colored product was collected, washed with H_2O (2 x 100 mL) and dried in a desiccator. It was coated onto SiO_2 (30 g) from DMF and flash chromatographed on SiO_2 (400 g) using 5% Et_3N , 10% MeOH, 85% CH_2Cl_2 as the eluant. Appropriate fractions were combined and evaporated to give the pure product (5.89 g) which was washed with Et_2O (50 mL). The column was next eluted with MeOH (1L), and the eluate was combined with the impure fractions and evaporated to give a residue which was coated onto SiO_2 (4.3 g) and flash chromatographed on SiO_2 (100 g) as before. Additional pure orange-colored product was thus obtained (0.41 g). The total yield was 6.3 g (42%), mp 271°C dec. NMR (Me_2SO-d_6) δ 3.03 (s, 3H, CH_3), 4.73 (s, 2H, CH_2), 7.28-7.38 (m, 3H, H^5, H^7, H^8), 7.42 (d, 2H, J = 8.3 Hz, aromatic), 7.48 (s, 1H, NH), 7.59-7.68 (m, 3H, aromatic), 7.90-7.95 (m, 4H, aromatic), 8.62 (br s, 1H, NH), 8.94 (br s, 1H, NH), 12.22 (br s, 1H, NH).

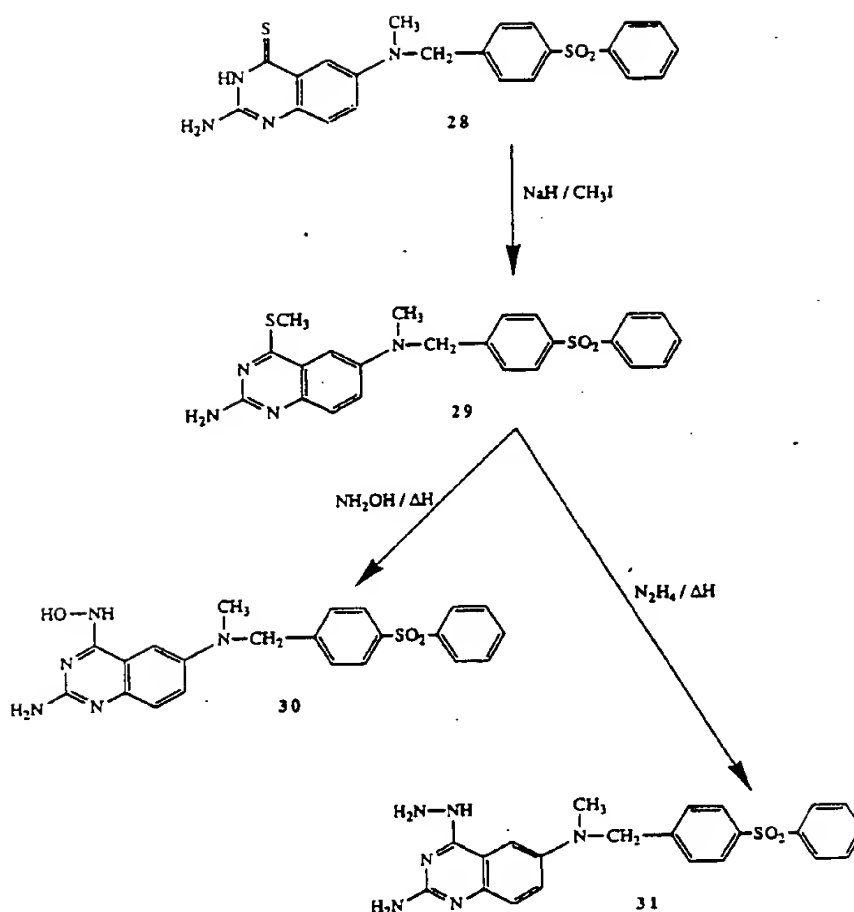
Anal., (C₂₂H₂₁N₅O₂S · 0.4 H₂O) C, H, N, S. HRMS (C₂₂H₂₁N₅O₂S)⁺ calcd, 419.1416; found, 419.1393.

Example 4: Preparation of Compounds 30 and 31

Compounds 30 and 31 were prepared according to the following reaction scheme:



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**Preparation of Compound (24) --
Methyl 5-Chloro-2-nitrobenzoate**

A solution of 5-chloro-2-nitrobenzoic acid (23, 201.6 g, 1 mol) and 50% BF₃·MeOH (250 mL, 1.5 mol) in MeOH (1100 mL) was heated at reflux for 26 h. The solution was cooled and basified to pH 8 with saturated NaHCO₃ and solid NaHCO₃, and extracted with CH₂Cl₂ (5 x 400 mL). The combined organic layers were washed with brine (800 mL), dried, and evaporated to give the product as an amber oil which solidified upon standing (177.5 g, 82%), mp 41-43°C. NMR (CDCl₃) δ 3.94 (s, 3H, CH₃), 7.59 (dd, 1H, J = 8.7, 2.2 Hz, H⁴), 7.68 (d, 1H, J = 2.2 Hz, H⁶), 7.92 (d, 1H, J = 8.7 Hz, H³). Anal. (C₈H₆ClNO₄) C, H, N, Cl.

Preparation of Compound (25) --
Methyl 5-(N-(4-(phenylsulfonyl)benzyl)
methylamino)-2-nitrobenzoate

A solution of N-methyl-4-(phenylsulfonyl)benzylamine (65.34 g, 0.25 mol), methyl 5-chloro-2-nitrobenzoate (53.90 g, 0.25 mol) and N,N-diisopropylethylamine (87 mL, 0.5 mol, 2 eq) in DMSO (350 mL) was heated at 90°C for 25 h. The mixture was poured into H₂O (3 L) and extracted with CH₂Cl₂ (2 x 400 mL). Solid NaCl was added to the aqueous layer which was extracted again with CH₂Cl₂ (2 x 400 mL). The organic layers were combined, dried, and evaporated under reduced pressure to leave an orange-colored residue. This was triturated vigorously with Et₂O (1 L), to give the product as a yellow-orange solid which was collected, washed with ether, and dried (41.9 g, 38%). An analytical sample was prepared by flash chromatography on SiO₂ using 50% hexane in EtOAc, mp 215.5-217.5°C. NMR (Me₂SO-d₆) satisfactory. Anal. (C₂₂H₂₀N₂O₆S) C, H, N, S.

Preparation of Compound (26) --
Methyl 2-amino-5-(N-(4-(phenylsulfonyl)
benzyl)methylamino)benzoate

A mixture of methyl 5-(N-(4-(phenylsulfonyl)benzyl)methylamino)-2-nitrobenzoate (41.9 g, 95 mmol) and CH₂Cl₂ (1.2 L) was gently warmed for 10 min to give a solution. CuCl (28.2 g, 285 mmol, 3 eq) was added in one portion followed by KBH₄ (35.9 g, 665 mmol, 7 eq) during 30 min; 15 min later further KBH₄ (5.12 g, 95 mmol, 1 eq) was added in one portion. After 50 min, the mixture was treated with charcoal and filtered. The filtrate was washed with brine (1.5 L), and the latter was back-extracted with CH₂Cl₂ (400 mL). The combined organic layers were treated with charcoal, dried, and evaporated under reduced pressure to give the technical grade product as an amber resin (35.0 g, 90%). A small portion was flash chromatographed on SiO₂ using 50% EtOAc in hexane as eluant to give the analytical sample as a sticky solid of indeterminate mp. NMR satisfactory. Anal. (C₂₂H₂₂N₂O₄S) C, H, N, S.

Preparation of Compound (27) --

2-Amino-3,4-dihydro-4-oxo-6-(N-(4-

(phenylsulfonyl)benzyl)methylamino)quinazoline

To a solution of methyl 2-amino-5-(N-(4-(phenylsulfonyl)benzyl)methylamino)benzoate (35.0 g, 85.3 mmol) in diglyme (105 mL) was added chlorformamidine hydrochloride (14.50 g, 128 mmol, 1.5 eq), and the resulting slurry was heated at 130°C for 1 h. The mixture was poured into a mixture of 1 N HCl (500 mL) and EtOH (800 mL) and gently heated to give a dark brown solution which was treated with charcoal and filtered. The filtrate was basified to pH 9 with NH_4OH to precipitate a yellow solid which was filtered off, washed with water, and dried in a desiccator to give a technical grade product (20.17 g, 56%). Chromatography of a small portion on SiO_2 using 5% Et_3N , 15% MeOH, 80% CH_2Cl_2 as eluant gave an analytical sample, mp 220°C dec. NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.00 (s, 3H, CH_3), 4.64 (s, 2H, CH_2), 6.08 (s, 2H, NH_2), 7.02 (d, 1H, $J = 2.8$ Hz, H^5), 7.06 (d, 1H, $J = 8.5$ Hz, H^8), 7.12 (dd, 1H, $J = 8.5, 2.8$ Hz, H^7), 7.42 (d, 2H, $J = 8.3$ Hz, aromatic), 7.57-7.77 (m, 3H, aromatic), 7.89-7.95 (m, 4H, aromatic), 10.90 (s, 1H, NH). Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3\text{S} \cdot 0.9 \text{H}_2\text{O}$) C, H, N, S. HRMS ($\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$)⁺ calcd, 420.1256; found, 420.1278.

Preparation of Compound (28) --

2-Amino-3,4-dihydro-6-(N-(4-(phenylsulfonyl)benzyl)

methylamiono)-4-thioquinazoline

To a solution of purified P_4S_{10} (0.026 g, 0.058 mmol 1 eq) in HMPA (0.5 mL) was added 2-amino-3,4-dihydro-4-oxo-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline (0.058 g, 0.1189 mmol) and the resulting solution was stirred at 110°C for 7 h. The brown solution was poured into NH_4OH (30 mL) and extracted with EtOAc (3 x 15 mL), and CH_2Cl_2 (15 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (30 mL), dried, and evaporated to give a yellow oil which was flash chromatographed on SiO_2 (8 g) using EtOAc as eluant to give a yellow solid of technical

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quality (0.014 g, 27%). NMR ($\text{Me}_2\text{SO}-d_6$) δ 12.32 (br s, 1H, thiolactam NH) plus all other signals as expected.

Preparation of Compound (29) --

2-Amino-4-(methylthio)-6-(N-(4-

(phenylsulfonyl)benzyl)methylamino)quinazoline

60% NaH in mineral oil (0.23 g, 5.73 mmol, 1 eq) in a 500 mL flame-dried flash was washed with hexanes (3 x 15 mL). A solution of 2-amino-3,4-dihydro-6-(N-(4(phenylsulfonyl)benzyl)methylamino)-4-thioquinazoline (2.50 g, 5.73 mmol) in a mixture of THF (100 mL) and DMF (10 mL), precooled to 0°C, was cannulated in during 5 min, and the mixture was stirred at 0°C for 45 min under argon. A solution of MeI (0.36 mL, 5.73 mmol, 1 eq) in THF (10 mL) was cannulated in one portion, and the cooling bath was then removed. The mixture was stirred for 15 min, poured into saturated brine (500 mL), and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with H_2O (500 mL), brine (500 mL), dried, and evaporated to give the technical grade product (2.46 g, 95%). Flash chromatography on SiO_2 using EtOAc gave an analytically pure sample as a yellow solid, mp 196-198°C. NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory. Anal. ($\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$) C, H, N, S.

Preparation of Compound (30) --

2-Amino-4-(hydroxyamino)-6-(N-(4-

(phenylsulfonyl)benzyl)methylamino)quinazoline

Hydroxylamine hydrochloride (0.382 g, 5.5 mmol, 5 eq) and N,N-diisopropylethylamine (1.15 mL, 6.6 mmol, 6 eq) dissolved in MeOH (3 mL) was added to a solution of 2-amino-4-(methylthio)-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)-quinazoline (0.5 g, 1.1 mmol) in THF (4 mL). The resulting solution was stirred in a pressure tube at 55°C for 1 h and then at 100°C for 3 h. A yellow solid precipitate formed which was filtered off, washed sequentially with CH_2Cl_2 , hexane, H_2O , and THF, and dried in a desiccator (320 mg, 66%), mp 250-251°C dec. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.95 (s, 3H, CH_3), 4.58 (s, 2H, CH_2), 6.05 (s, 2H, NH_2), 6.83 (s, 3H, H^5 , H^7 , H^8), 7.40 (d, 2H, $J = 8.3$, aromatic), 7.58-7.70 (m, 3H, aromatic), 7.89-7.95 (m, 4H, aromatic), 9.58 (br s, 1H,

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hydroxylamino proton), 9.86 (br, 1H, hydroxylamino proton).
Anal. ($C_{22}H_{21}N_5O_3S$) C,H,N,S. The HRMS sample was purified by flash chromatography on SiO_2 using EtOAc to elute a trace of starting material followed by DMF to elute the desired product: ($C_{22}H_{21}N_5O_3S$)⁺ calcd, 435.1365; found, 435.1347

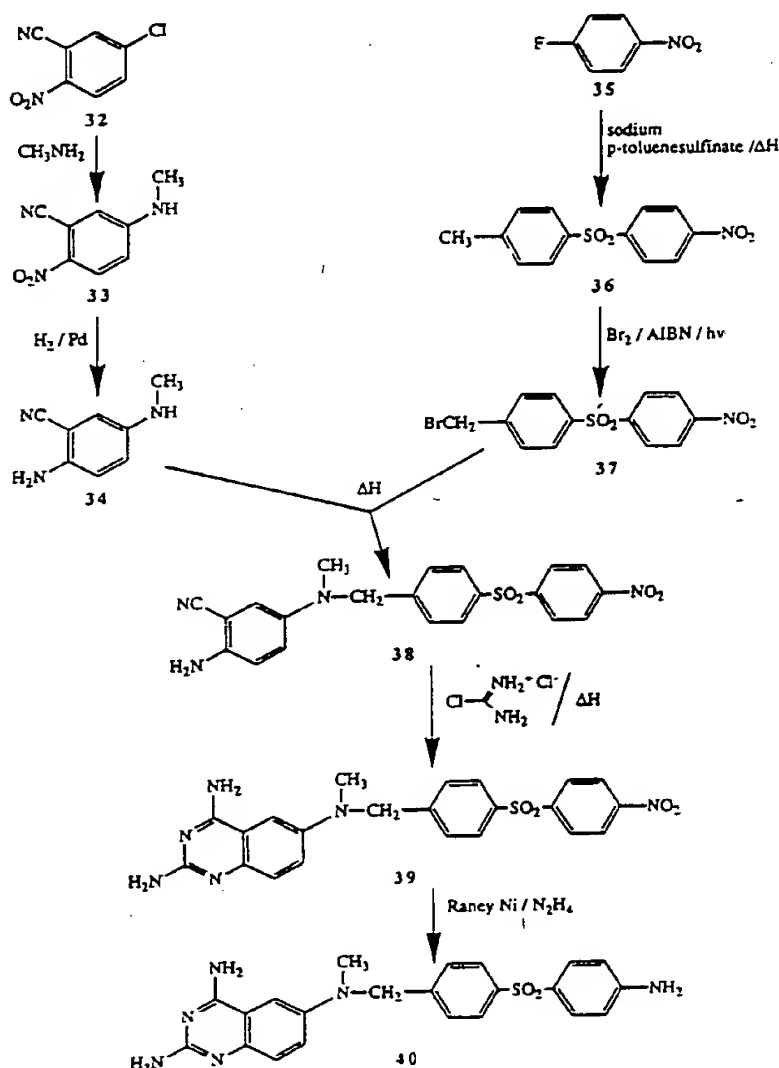
Preparation of Compound (31) --

2-Amino-4-hydrazino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

A mixture of 2-amino-4-(methylthio)-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline (0.5 g, 1.1 mmol), anhydrous hydrazine (0.34 mL, 11 mmol, 10 eq), MeOH (4 mL) and THF (1 mL) was stirred as a solution in a pressure tube at 140°C for 2.5 h. The solvent was evaporated under reduced pressure to give a residue which was dissolved in a minimum of CH_2Cl_2 to which hexane was added to precipitate an orange-colored solid which was filtered off, washed with hexane, and dried in a desiccator (320 mg, 67%), mp 188°C dec. NMR (Me_2SO-d_6) δ 2.93 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 5.89 (s, 2H, NH_2), 7.07-7.11 (m, 3H, H^5, H^7, H^8), 7.42 (d, 2H, $J = 8.3$ Hz, aromatic), 7.57-7.70 (m, 3H, aromatic), 7.89-7.95 (m, 4H, aromatic), hydrazino signals not visible. Anal. ($C_{22}H_{22}N_6O_2S \cdot 0.6 H_2O$) C,H,N,S. HRMS ($C_{22}H_{22}N_6O_2S$)⁺ calcd, 434.1525; found, 434.1529.

Example 5: Preparation of Compounds 39 and 40

Compounds 39 and 40 were prepared according to the following reaction scheme:



**Preparation of Compound (33) --
5-(Methylamino)-2-nitrobenzonitrile**

(a) A solution of 5-chloro-2-nitrobenzonitrile (32, 10.04 g, 0.055 mol) and 40% w/w aqueous methylamine (94 mL, 1.1 mol, 20 eq) in DMSO (60 mL) was heated at 70°C for 1.5 h under a dry ice condenser. The resulting dark red-brown solution was poured into H_2O (800 mL) and extracted with

EtOAc (400 mL). Solid NaCl was added to the aqueous layer which was again extracted with EtOAc (400 mL). The organic layers were combined, dried, and evaporated to give a crude, sticky, orange-brown solid which was dissolved in acetone (20 mL) for flash chromatography on SiO₂ (400 g), eluting first with 50% EtOAc in hexane then with EtOAc. A pure orange-colored solid product was thus obtained (8.4 g, 86%), mp 203-204°C. NMR (Me₂SO-d₆) δ 2.84 (d, 3H, J = 4.9 Hz, CH₃), 6.85 (dd, 1H, J = 9.4, 2.6 Hz, H⁴), 7.06 (d, 1H, J = 2.6 Hz, H⁶), 7.75 (d, 1H, J = 4.9 Hz, NH), 8.14 (d, 1H, J = 9.4 Hz, H³). Anal. (C₈H₇N₃O₂) C, H, N.

(b) A solution of 5-chloro-2-nitrobenzonitrile (36.51 g, 0.2 mol) and 40% ^{w/w} aqueous methylamine (258 mL, 3 mol, 15 eq) in DMSO (150 mL) was heated at 70°C for 1 hr under a dry ice condenser. The resulting dark red-brown solution was poured into brine (2 L) and extracted with EtOAc (3 x 500 mL). The combined extracts were dried and evaporated to give the crude product as a sticky, brown solid. This was shaken with Et₂O (50 mL), filtered off, washed with Et₂O (50 mL), and dried to give a pale orange-colored solid (27.18 g, 77%) pure by TLC (SiO₂ - 50% EtOAc in hexane).

Preparation of Compound (34) --

2-Amino-5-(methylamino)benzonitrile

A partial suspension of 5-(methylamino)-2-nitrobenzonitrile (7.41 g, 0.042 mol) in a mixture of EtOH (180 mL) and THF (50 mL) containing 10% Pd:C catalyst (0.74 g) was stirred under hydrogen at atmospheric pressure for 4 h. The resulting solution was filtered through celite. The celite bed was washed with EtOAc (250 mL), and the combined filtrates were evaporated to give a quantitative yield of the product as a dark oil suitable for further use. Flash chromatography on SiO₂ using 50% EtOAc in hexane as eluant afforded an analytical sample as a pale yellow oil which solidified upon standing, mp 64-65°C, NMR (Me₂SO-d₆) δ 2.58 (s, 3H, CH₃), 5.16 (br s, 3H, NH & NH₂), 6.43 (d, 1H, J = 2.6 Hz, H⁶), 6.66 (d, 1H, J = 8.9 Hz, H³), 6.72 (dd, 1H, J = 8.9, 2.6 Hz, H⁴). Anal. (C₈H₉N₃) C, H, N.

Preparation of Compound (36) --

4-Nitrophenyl p-tolylsulfone

A mixture of sodium p-toluensulfinate (53.46 g, 0.3 mol) and 1-fluoro-4-nitrobenzene (35, 35.0 mL, 0.33 mol, 1.1 eq) in DMSO (300 mL) was heated at 130°C for 2 h 45 min, during which time a very fine precipitate of NaF formed. The mixture was then allowed to cool slowly overnight to 25°C whereupon large crystals of product appeared. The supernatant was decanted from the crystals which were then washed with EtOH (2 x 50 mL) to carry away the fine NaF residues. The pale yellow crystals were next washed sequentially with water (150 mL), Et₂O (100 mL) and hexanes (100 mL) to yield product (41.8 g). Additional product (9.2 g) was obtained by pouring the DMSO layer into water (2400 mL), filtering off the resulting solid, and washing it with Et₂O (125 mL) and then hexane (125 mL). TLC (SiO₂/1:1 EtOAc:hexane) showed that both crops of product were of technical quality and suitable for further use (51.0 g, 61%). NMR satisfactory.

Preparation of Compound (37) --

4-((4-Nitrophenyl)sulfonyl)benzyl bromide

A solution of 4-nitrophenyl p-tolylsulfone (24.95 g, 0.09 mol) in benzene (150 mL) in contact with water (50 mL) was stirred vigorously at reflux. A few granules of AIBN were added, and the mixture, under irradiation from a 200 watt bulb, was treated with bromine (4.7 mL, 0.09 mol, 1 eq) in benzene (40 mL) dropwise at a rate such that the reaction mixture did not turn too red. This addition took 50 min. The mixture was removed from the heat, and the water layer was removed immediately by pipet. The organic phase was cooled overnight to give the crystalline product which was filtered off and washed with benzene (2 x 50 mL) and dried (21.7 g). TLC (SiO₂-25% EtOAc in hexane) showed about 80% purity and thus the yield was about 54%. A second crop, obtained from the dried, concentrated filtrate, was recrystallized from toluene to give a 50% product (2.8 g) which was discarded.

Preparation of Compound (38) --

2-Amino-5-(N-(4-((4-nitrophenyl)
(sulfonyl)benzyl)methylamino)benzonitrile

A solution of 2-amino-5-(methylamino)benzonitrile (5.99 g, 41 mmol), and 80% 4-((4-nitrophenyl)sulfonyl)benzyl bromide (19.93 g, 45 mmol, 1.1 eq), and N,N-diisopropyl ethylamine (7.8 mL, 45 mmol, 1.1 eq) in DMA (100 mL) was stirred under argon at 110°C for 50 min. The mixture was poured into H₂O (1500 mL) and extracted with EtOAc (3 x 200 mL). The organic layers were combined, dried, and evaporated to give a brown sludge which was chromatographed on SiO₂ (700 g) using 50% EtOAc in hexane as eluant. The best fractions gave partially purified product (15.24 g) which was rechromatographed on SiO₂ (500 g) using 40% EtOAc in hexane to give purified product (6.12 g). One of the best fractions from this chromatography was evaporated separately to give the analytical sample as a dark brown solid (0.26 g); total yield 36.8%, mp 164-166°C, NMR (Me₂SO-d₆) δ 2.81 (s, 3H, CH₃), 4.48 (s, 2H, CH₂), 5.34 (s, 2H, NH₂), 6.69 (m, 2H, H³ & H⁶), 6.92 (dd, 1H, J = 9.1, 3.0 Hz, H⁴), 7.44 (d, 2H, J = 8.4 Hz, aromatic), 7.96 (d, 2H, J = 8.4 Hz, aromatic), 8.21 (2H, J = 9.0 Hz, aromatic), 8.39 (2H, d, J = 9.0 Hz, aromatic). Anal. (C₂₁H₁₈N₄O₄S) C, H, N, S.

Preparation of Compound (39) --

2,4-Diamino-6-(N-(4-((4-nitrophenyl)
sulfonyl)benzyl)methylamino)quinazoline

A solution of 2-amino-5-(N-(4-((4-nitrophenyl)sulfonyl)-benzyl)methylamino)benzonitrile (6.12 g, 14 mmol) and chlorformamidine hydrochloride (2.00 g, 17.4 mmol, 1.24 eq) in diglyme (35 mL) was heated at 115°C. At 1 h, 20 min, additional chlorformamidine hydrochloride (0.16 g, 0.1 eq) was added. At 1.5 h, the reaction mixture was removed from the heat and allowed to cool to 25°C. The diglyme layer was decanted to leave a brown gummy residue which was warmed with DMF (20 mL) to give a solution to which Et₃N (10 mL, 5 eq) was added. The resulting mixture was poured into H₂O (900 mL) and extracted with EtOAc (2 x 300 mL). The aqueous layer

was combined with saturated brine (500 mL) and extracted once more with EtOAc (300 mL). The organic layers were combined, dried, treated with charcoal, filtered, and evaporated to give the crude product as a dark brown viscous sludge (5.34 g). TLC (SiO_2 - 5% Et_3N /10% MeOH /85% CH_2Cl_2) of the diglyme layer showed essentially no desired product, and it was thus discarded. The crude product was chromatographed on SiO_2 (400 g) with 5% Et_3N /10% MeOH /85% CH_2Cl_2 as eluant to give the pure product as a brown solid (2.18 g, 32%), mp 234°C dec, NMR ($\text{Me}_2\text{SO}-d_6$ δ 2.96 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 6.09 (s, 2H, NH_2), 7.10-7.19 (m, 3H, H^5 , H^7 , H^8), 7.48 (d, 4H, J = 8.4 Hz, NH_2 & aromatic), 7.98 (d, 2H, J = 8.4 Hz, aromatic), 8.21 (d, 2H, J = 8.9 Hz, aromatic), 8.38 (d, 2H, J = 8.9 Hz, aromatic). Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_6\text{O}_4\text{S} \cdot 0.8 \text{H}_2\text{O}$), C, H, N, S. HRMS ($\text{C}_{22}\text{H}_{20}\text{N}_6\text{O}_4\text{S}$)⁺ calcd, 464.1267; found, 464.1241.

Preparation of Compound (40) --

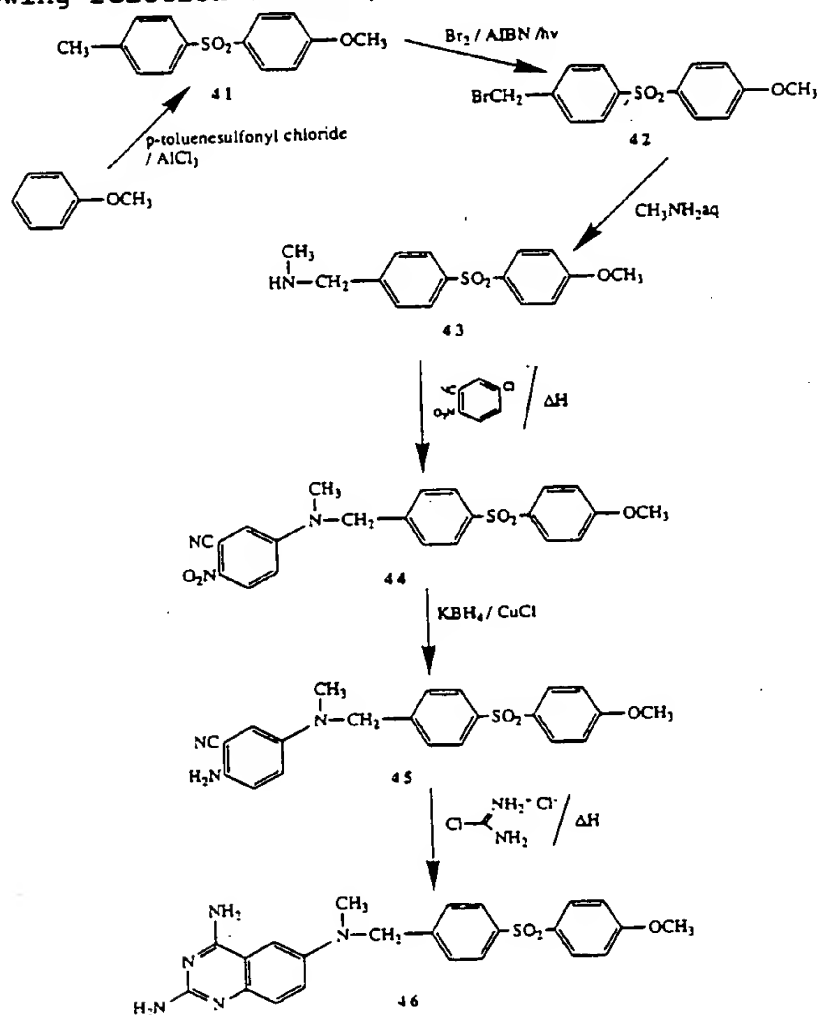
2,4-Diamino-6-(N-(4-((4-aminophenyl)sulfonyl)
benzyl)methylamino)quinazoline

A solution of 2,4-diamino-6-(N-4((4-nitrophenyl)sulfonyl)-benzyl)methylamino)quinazoline (1.21 g, 2.6 mmol) in EtOH (220 mL) was brought to reflux when Raney nickel (0.15 g) and hydrazine (0.41 mL, 13 mmol, 5 eq) were added. At 20 min, additional hydrazine (0.41 mL); at 35 min, additional hydrazine (0.41 mL) plus catalyst (0.30 g); and at 50 min, additional hydrazine (0.41 mL) plus catalyst (0.30 g) were added to ensure complete conversion. At 60 min, the light yellow solution was cooled and filtered through celite, and the celite was washed with EtOH (30 mL). The combined filtrates were evaporated to give a crude yellow solid (1.2 g) which was chromatographed on SiO_2 (100 g) using 5% Et_3N /15% MeOH /80% CH_2Cl_2 as eluant to give the purified product as a dull yellow solid (0.18 g). The mixed fractions were combined, concentrated, and re-chromatographed as above on SiO_2 (75 g) to give additional product (0.14 g), total yield 29%. Since both samples had a trace impurity by TLC (SiO_2 - 5% Et_3N /10% MeOH /85% CH_2Cl_2), they were combined and given a final chromatography on basic alumina (55 g) using 12.5% MeOH

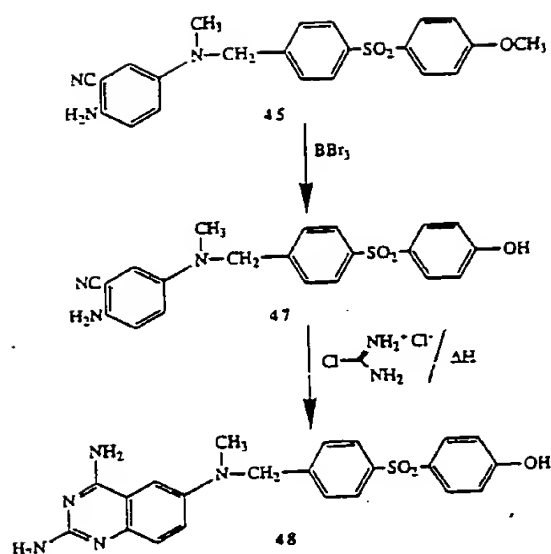
in CH_2Cl_2 as eluant to give a lemon-yellow solid (0.159 g), mp 164-166°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.91 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.67 (s, 2H, NH_2), 6.16 (s, 2H, NH_2), 6.59 (d, 2H, $\text{J} = 8.7$ Hz, aromatic), 7.07-7.18 (m, 5H, H^5 , H^7 , H^8 , & NH_2), 7.38 (d, 2H, $\text{J} = 8.3$ Hz, aromatic), 7.52 (d, 2H, $\text{J} = 8.7$ Hz, aromatic), 7.76 (d, 2H, $\text{J} = 8.3$ Hz, aromatic), Anal. ($\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_2\text{S} \cdot 0.5 \text{H}_2\text{O}$) C, H, N, S. HRMS ($\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_2\text{S}$)⁺ calcd, 434.1525; found, 434.1538.

Example 6: Preparation of Compounds 46 and 48

Compounds 46 and 48 were prepared according to the following reaction scheme:



-48-



Preparation of Compound (41) --

4-Methoxyphenyl p-tolyl sulfone

4-Methoxyphenyl p-tolyl sulfone (41) was prepared by a published method [H. Burton and P.F. Hu, *J. Chem. Soc.*, 601 (1948)] conducted on the same scale (0.21 mol). The yield of the pure desired para isomer was 35%.

Preparation of Compound (42) --

4-((4-Methoxyphenyl)sulfone)benzyl bromide

A solution of 4-methoxyphenyl p-tolyl sulfone (20.00 g, 0.076 mol) in benzene (125 mL) in contact with water (40 mL) was stirred vigorously at reflux. A few granules of AIBN were added, and the mixture was irradiated with a 200 watt bulb and treated dropwise during 20 min with bromine (3.9 mL, 0.076 mol, 1 eq) in benzene (30 mL). The colorless reaction mixture was removed from the heat, the water layer immediately removed by pipet, and CH_2Cl_2 (250 mL) added to the organic phase. The solution was dried and evaporated to give the crude product as a white solid which was used without further purification. Approximate yield 60%.

Preparation of Compound (43) --

N-Methyl-4-((4-methoxyphenyl)sulfonyl)benzylamine

To a 40% ^w/_w aqueous methylamine solution (12.9 mL, 9.15 mol, 15 eq) in THF (5 mL) was added a solution of the crude 4-((4-methoxyphenyl)sulfonyl)benzyl bromide (approx 4.5 g) in THF (28 mL) during 5 min. The mixture was stirred for an additional 20 min, poured into H₂O (200 mL), and extracted with CH₂Cl₂ (2 x 50 mL). The combined extracts were washed with H₂O (200 mL) and then shaken with 2N HCl (100 mL). The acid layer was removed, washed with CH₂Cl₂ (50 mL), and then basified to pH 12 with 2N NaOH (100 mL). The product thus released was extracted with CH₂Cl₂ (2 x 50 mL), and the extracts were combined, dried, and evaporated to give an amber oil which solidified upon standing (1.64 g, 56%). An analytical sample was prepared by recrystallization from EtOH/H₂O, mp 88-89.5°C, NMR (Me₂SO-d₆) δ 2.21 (s, 3H, N-CH₃), 3.67 (s, 2H, CH₂), 3.81 (s, 3H, O-CH₃), 7.12 (d, 2H, J = 8.9 Hz, aromatic), 7.53 (d, 2H, J = 8.4 Hz, aromatic), 7.84 (d, 2H, J = 8.4 Hz, aromatic), 7.86 (d, 2H, J = 8.9 Hz, aromatic). Anal. (C₁₅H₁₇NO₃S) C, H, N, S.

Preparation of Compound (44) --

5-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)-2-nitrobenzonitrile

A mixture of N-methyl-4-((4-methoxyphenyl)sulfonyl)benzylamine (6.12 g, 0.021 mol), 5-chloro-2-nitrobenzonitrile (4.27 g, 0.023 mol, 1.1 eq), and N,N-diisopropylethylamine (5.5 mL, 1.5 eq) in DMSO (45 mL) was stirred at 85°C. At 3 h, CaCO₃ (2.1 g, 1 eq) was added and heating continued for 15 h. The mixture was cooled and filtered through celite and the filtrate was poured into H₂O (1200 mL) and extracted with EtOAc (2 x 200 mL). The organic layers were combined, dried, and evaporated to give a crude orange-brown solid. This was suspended in boiling EtOH (125 mL), shaken vigorously, and cooled. The analytically-pure, yellow-orange product was filtered off and washed with cold EtOH (125 mL) and dried (7.69 g, 84%), mp 181-183°C. NMR (Me₂SO-d₆) δ 3.21 (s, 3H, N-CH₃), 3.81 (s, 3H, O-CH₃), 4.91 (s, 2H, CH₂), 7.00 (dd, 1H,

$J = 9.6, 2.9 \text{ Hz, H}^4$), 7.12 (d, 2H, $J = 9.0 \text{ Hz, aromatic}$), 7.36 (d, 1H, $J = 2.9 \text{ Hz, H}^6$), 7.38 (d, 2H, $J = 8.4 \text{ Hz, aromatic}$), 7.84-7.91 (m, 4H, aromatic), 8.15 (d, 1H, $J = 9.6 \text{ Hz, H}^3$). Anal. ($\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$) C, H, N, S.

Preparation of Compound (45) --

2-Amino-5-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)benzonitrile

To a solution of 5-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)-2-nitrobenzonitrile (7.69 g, 18 mmol) in CH_2Cl_2 (400 mL) was added MeOH (400 mL) and CuCl (5.34 g, 54 mmol, 3 eq). KBH_4 (6.80 g, 126 mmol, 7 eq) was added during 10 min at 25°C, and the mixture was stirred for an additional 10 min. Black copper salts were filtered off and discarded. The filtrate was washed with H_2O (1200 mL), dried, and evaporated to give a crude brown residue. This was coated onto SiO_2 (50 g) from CH_2Cl_2 and flash chromatographed on SiO_2 (400 g) eluting with 30% hexane in EtOAc to give the purified product as a sticky yellow solid (3.50 g, 49%), mp 48°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.80 (s, 3H, N- CH_3), 3.81 (s, 3H, O- CH_3), 4.45 (s, 2H, CH_2), 5.34 (br s, 2H, NH_2), 6.69 (m, 2H, H^3 & H^6), 6.93 (dd, 1H, $J = 9.1, 3.0 \text{ Hz, H}^4$), 7.11 (d, 2H, $J = 9.0 \text{ Hz, aromatic}$), 7.38 (d, 2H, $J = 8.4 \text{ Hz, aromatic}$), 7.84-7.88 (m, 4H, aromatic). Anal. ($\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$) C, H, N, S.

Preparation of Compound (46) --

2,4-Diamino-6-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)quinazoline

To a solution of 2-amino-5-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)benzonitrile (1.50 g, 3.7 mmol) in diglyme (15 mL) was added chlorformamidinium hydrochloride (0.51 g, 4.4 mmol, 1.2 eq). The mixture was heated at 115°C for 45 min and let cool to 25°C. The diglyme layer was decanted from the brown resin which had formed. This resin was dissolved in DMF (7 mL), treated with Et_3N (2.6 mL, 18.5 mmol, 5 eq), and the resulting solution was poured into H_2O (300 mL) and extracted with EtOAc (100 mL). To the aqueous layer was added saturated brine (100 mL), and it was further extracted with EtOAc (100 mL). The combined

extracts were dried and evaporated to give an orange-colored solid which was coated onto alumina (10 g) and chromatographed on alumina (200 g) with 10% MeOH in CH_2Cl_2 as eluant to give the pure product as a lemon-yellow solid (0.33 g, 20%), mp 271-272°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.92 (s, 3H, N- CH_3), 3.81 (s, 3H, O- CH_3), 4.62 (s, 2H, CH_2), 5.59 (s, 2H, NH_2), 7.05-7.16 (m, 7H, NH_2 , H^5 , H^7 , H^8 , & aromatic), 7.42 (d, 2H, $J = 8.4$ Hz, aromatic), 7.86 (m, 4H, aromatic). Anal. ($\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_3\text{S} \cdot 0.5 \text{H}_2\text{O}$) C, H, N, S. HRMS ($\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$)⁺ calcd, 449.1522; found, 449.1529.

An alternative annelation process for preparing this compound using cyanamide as the reagent is described on page 124 and 125.

Preparation of Compound (47) --

2-Amino-5-(N-(4-((4-hydroxyphenyl)sulfonyl)benzyl)methylamino)benzonitrile

A solution of 2-amino-5-(N-(4-((4-methoxyphenyl)sulfonyl)benzyl)methylamino)benzonitrile (1.85 g, 4.6 mmol) in CH_2Cl_2 (25 mL) was warmed to 40°C under N_2 . BBr_3 (1M in CH_2Cl_2 , 18.4 mL, 18.4 mmol, 4 eq) was added during 5 min. A fine suspension formed, and the mixture was then heated at 60°C. At 1 h 50 min, additional reagent (4.6 mL, 1 eq) was added. At 2.5 h, the mixture was poured into H_2O (300 mL) and extracted with EtOAc (100 mL). Solid NaCl was added to the aqueous layer, and it was extracted once more with EtOAc (100 mL). The extracts were combined, dried, and evaporated to give an orange-colored solid suitable for further use (970 mg, 55%). An analytical sample was prepared by chromatography on SiO_2 with 50% EtOAc in hexane as eluant, mp 65-70°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.80 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 5.39 (br s, 2H, NH_2), 6.70 (m, 2H, aromatic), 6.92 (m, 3H, aromatic), 7.38 (d, 2H, $J = 8.4$ Hz, aromatic), 7.74 (d, 2H, $J = 8.8$ Hz, aromatic), 7.82 (d, 2H, $J = 8.4$ Hz, aromatic), 10.63 (s, 1H, OH). Anal. ($\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$) C, H, N, S.

Preparation of Compound (48) --

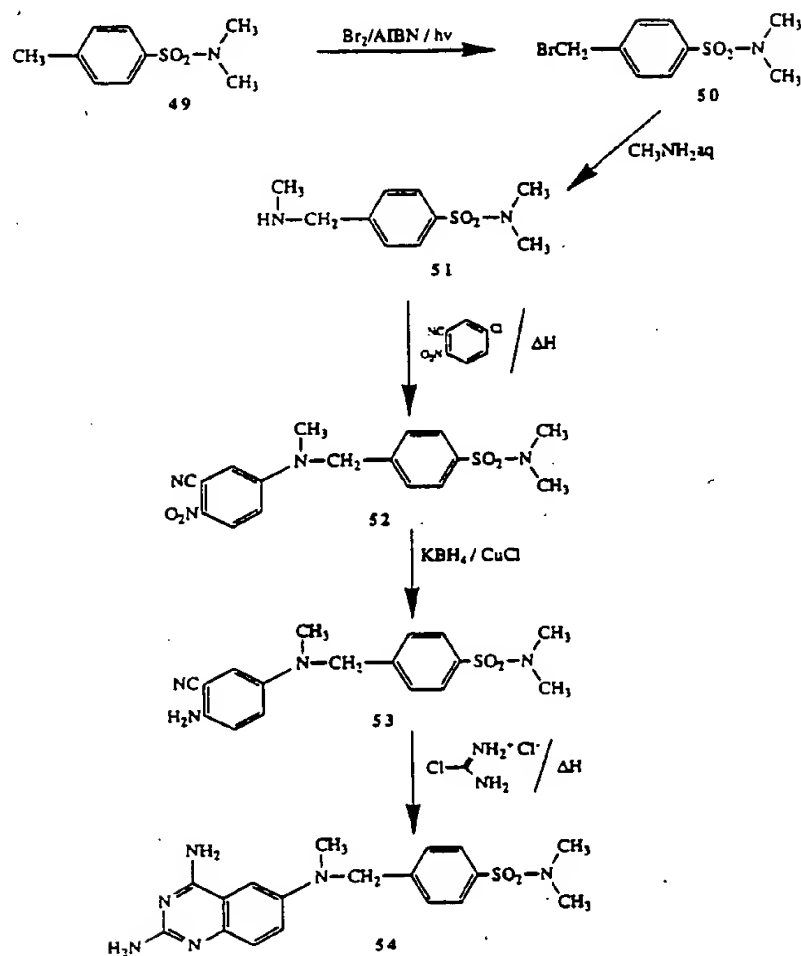
2,4-Diamino-6-(N-(4-((4-hydroxyphenyl)sulfonyl)
benzyl)methylamino)quinazoline

A mixture of 2-amino-5-(N-(4-((4-hydroxyphenyl)sulfonyl)benzyl)methylamino)benzonitrile (0.92 g, 2.34 mmol), chlorformamidinium hydrochloride (0.32 g, 2.8 mmol, 1.2 eq), and diglyme (15 mL) was heated at 125°C for 55 min and let cool to 25°C. The diglyme layer was decanted, and the remaining brown resin was dissolved in DMF (5 mL), treated with Et₃N (1.63 mL, 5 eq), and poured into H₂O (100 mL). The mixture was extracted with EtOAc (2 x 50 mL) followed by n-BuOH (2 x 50 mL). The four extracts were combined, dried, and evaporated to give a crude orange-colored solid. This was coated onto silica (5 g) from DMF and chromatographed on SiO₂ (50 g) using 5% Et₃N/20%MeOH/75%CH₂Cl₂ as eluant to give the pure product as a yellow solid (105 mg, 10%), mp 193°C dec. NMR (Me₂SO-d₆) δ 2.92 (s, 3H, CH₃), 4.61 (s, 2H, CH₂), 5.66 (s, 2H, NH₂), 6.90 (d, 2H, J = 8.9 Hz, aromatic), 7.06-7.17 (m, 5H, H⁵, H⁷, H⁸, & NH₂), 7.40 (d, 2H, J = 8.4 Hz, aromatic), 7.74 (d, 2H, J = 8.9 Hz; aromatic), 7.82 (d, 2H, J = 8.4 Hz, aromatic), OH not visible. Anal. (C₂₂H₂₁N₅O₃S · 1.4 H₂O) C, H, N, S. HRMS (C₂₂H₂₁N₅O₃S)⁺ calcd, 435.1365; found, 435.1374.

An alternative annelation process for preparing this compound using cyanamide as the reagent is described on page 124 and 125.

Example 7: Preparation of Compound 54

Compound 54 was prepared according to the following reaction scheme:

**Preparation of Compound (50) --****4-(N,N-Dimethylsulfamoyl)benzyl bromide**

A solution of N,N-dimethyl-p-toluenesulfonamide (49, 20.0 g, 100 mmol) in C_6H_6 (120 mL) in contact with H_2O (40 mL) was stirred vigorously at reflux. A few granules of AIBN were added, and the mixture, irradiated with a 200 watt bulb,

was treated dropwise with bromine (5.2 mL, 100 mmol, 1 eq) in C_6H_6 (40 mL) during 15 min. Heating of the colorless mixture was stopped, and the aqueous layer was immediately removed by pipet and CH_2Cl_2 (200 mL) added to the organic layer. The organic phase was dried and evaporated to give the crude product as an amber-colored oil (24.3 g) which slowly solidified upon standing and which was used without further purification.

Preparation of Compound (51) --

N-Methyl-4-(N,N-dimethylsulfamoyl)benzylamine

To a 40% w/w aqueous methylamine solution (78 mL, 0.92 mol, about 15 eq) in THF (20 mL) was added a solution of the crude 4-(N,N-dimethylsulfamoyl)benzyl bromide (24.3 g) in THF (120 mL) during 15 min. The mixture was poured into H_2O (800 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined extracts were washed with H_2O (800 mL) and then shaken with 2N HCl (300 mL). The acid layer was removed, washed with CH_2Cl_2 (100 mL), and basified to pH 12 with 2N NaOH (300 mL). The product thus released was extracted with CH_2Cl_2 (2 x 200 mL), and the extracts were combined, dried, and evaporated to give a beige-colored solid of technical quality (8.48 g, 37% overall from N,N-dimethyl-p-toluenesulfonamide). An analytical sample was prepared by chromatography on SiO_2 using 3% Et_3N in CH_3CN as eluant, mp 82-84°C. NMR (Me_2SO-d_6) δ 2.26 (s, 3H, N- CH_3), 2.58 (s, 6H, N- Me_2), 3.73 (s, 2H, CH_2), 7.58 (d, 2H, J = 8.3 Hz, aromatic), 7.68 (d, 2H, J = 8.3 Hz, aromatic), NH not visible. Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N, S.

Preparation of Compound (52) --

5-(N-(4-(N,N-Dimethylsulfamoyl)benzyl)
methylamino)-2-nitrobenzonitrile

A mixture of N-methyl-4-(N,N-dimethylsulfamoyl)benzylamine (8.48 g, 37 mmol), 5-chloro-2-nitrobenzonitrile (7.46 g, 41 mmol, 1.1 eq), and $CaCO_3$ (4.46 g, 45 mmol, 1.2 eq) in DMSO (45 mL) was stirred at 110-120°C for 5 h. The mixture was filtered through celite, and the filtrate was poured into H_2O (1200 mL) and extracted with EtOAc (200 mL).

Brine (400 mL) was added to the aqueous layer, and it was further extracted with EtOAc (2 x 200 mL). The combined extracts were dried and evaporated to give a residue which was shaken vigorously with hot EtOH (50 mL). The lemon-yellow solid which resulted was filtered off and washed with cold EtOH (100 mL) and dried; it was essentially pure by TLC ($\text{SiO}_2/\text{EtOAc}$) (6.32 g, 46%). An analytical sample was prepared by chromatography on SiO_2 using 10% hexane in EtOAc as eluant, mp 208.5-210.5°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.59 (s, 6H, N-Me₂), 3.25 (s, 3H, CH₃), 4.97 (s, 2H, CH₂), 7.05 (dd, 1H, J = 9.6, 3.0 Hz, H⁴), 7.38 (d, 1H, J = 3.0 Hz, H⁶), 7.44 (d, 2H, J = 8.3 Hz, aromatic), 7.74 (d, 2H, J = 8.3 Hz, aromatic), 8.18 (d, 1H, J = 9.6 Hz, H³). Anal. ($\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_4\text{S}$) C, H, N, S.

Preparation of Compound (53) --

2-Amino-5-(N-(4-(N,N-dimethylsulfamoyl)benzyl)methylamino)benzonitrile

To a solution of 5-(N-(4-(N,N-dimethylsulfamoyl)benzyl)methylamino)-2-nitrobenzonitrile (6.27 g, 17 mmol) in a mixture of CH_2Cl_2 (250 mL) and MeOH (250 mL) containing CuCl (4.97 g, 50 mmol, 3 eq) in suspension at 25°C was added KBH_4 (6.31 g, 117 mmol, 7 eq) during 5 min. The mixture was stirred for 15 min, and the black copper salts were filtered off, washed with CH_2Cl_2 (100 mL), and discarded. The combined filtrates were washed with H_2O (1200 mL), dried, and evaporated to give a crude, orange-colored, sticky solid which was chromatographed on SiO_2 (150 g) with 30% hexane in EtOAc to give the pure product as a pale yellow solid (3.09 g, 53%), mp 156-157°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.58 (s, 6H, N-Me₂), 2.84 (s, 3H, CH₃), 4.50 (s, 2H, CH₂), 5.36 (s, 2H, NH₂), 6.72 (m, 2H, H³ & H⁶), 6.98 (dd, 1H, J = 9.1, 3.0 Hz, H⁴), 7.44 (d, 2H, J = 8.3 Hz, aromatic), 7.70 (d, 2H, J = 8.3 Hz, aromatic). Anal. ($\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$) C, H, N, S.

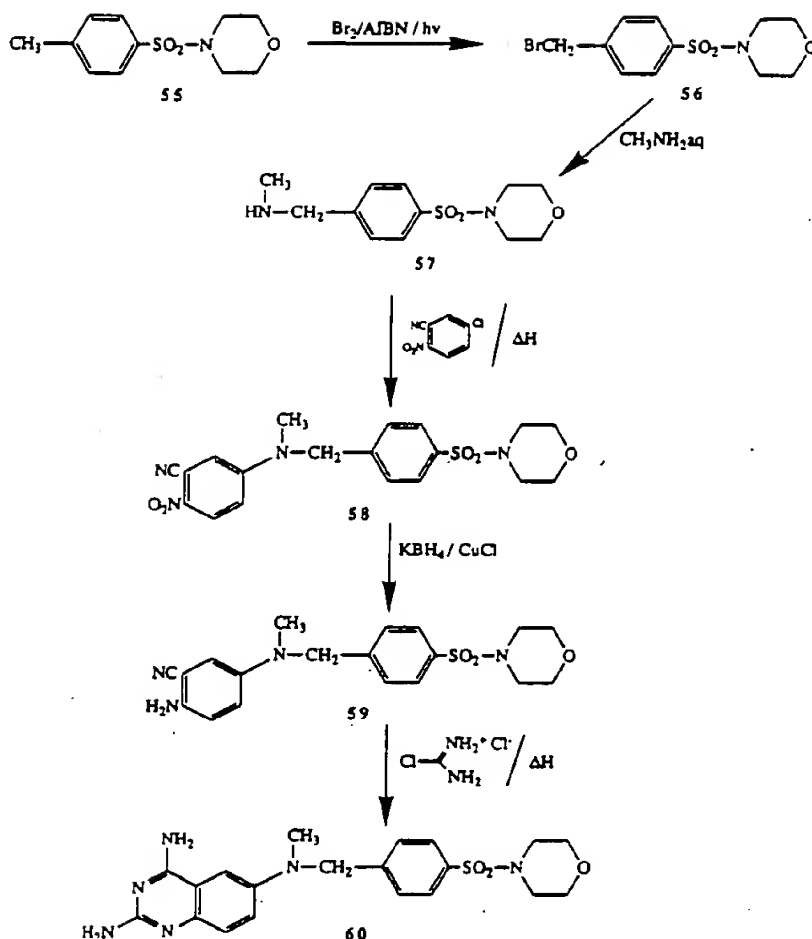
Preparation of Compound (54) --
2,4-Diamino-6-(N-(4-(N,N-dimethylsulfamoyl)
benzyl)methylamino)quinazoline

A mixture of 2-amino-5-(N-(4-(N,N-dimethylsulfamoyl)benzyl)-methylamino)benzonitrile (3.07 g, 8.9 mmol) in diglyme (30 mL) and chlorformamidinium hydrochloride (1.23 g, 10.7 mmol, 1.2 eq) was heated at 130°C for 35 min and cooled to 25°C. The diglyme layer was decanted from the brown gummy residue which had formed during the reaction. The residue was dissolved in DMF (25 mL) and treated with Et₃N (6.2 mL, 44 mmol, 5 eq), and the resulting solution was poured into H₂O (500 mL) and extracted with EtOAc (100 mL). Saturated brine (250 mL) was added to the aqueous layer, and it was extracted once more with EtOAc (150 mL). The extracts were combined, dried, evaporated, coated onto basic alumina (10 g) and chromatographed on basic alumina (200 g) with 7% MeOH in CH₂Cl₂ as eluant to give the product which was recrystallized from EtOH/H₂O as a pale yellow solid (0.524 g, 15.2%), mp 256.5-258.5°C. NMR (Me₂SO-d₆) δ 2.58 (s, 6H, N-Me₂), 2.96 (s, 3H, CH₃), 4.67 (s, 2H, CH₂), 5.64 (s, 2H, NH₂), 7.09-7.22 (m, 5H, H⁵, H⁷, H⁸ & NH₂), 7.48 (d, 2H, J = 8.3 Hz, aromatic), 7.70 (d, 2H, J = 8.3 Hz, aromatic). Anal. C₁₈H₂₂N₆O₂S · 1.2 H₂O C, H, N, S. HRMS (C₁₈H₂₂N₆O₂S)⁺ calcd, 386.1525; found, 386.1541.

Example 8: Preparation of Compound 60

Compound 60 was prepared according to the following reaction scheme:

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Preparation of Compound (56) --

4-(Morpholinosulfonyl)benzyl bromide

A solution of N-(p-toluenesulfonyl)morpholine (55, 10.00 g, 41 mmol) in CCl_4 (90 mL) was heated to reflux. N-bromosuccinimide (8.85 g, 49 mmol 1.2 eq) was added, and the mixture, under reflux, was irradiated with a 200 watt bulb for 45 min. The organic phase was extracted with H_2O (400 mL), dried, and evaporated to give the crude product as a

beige solid which was used without purification (14 g). It contained about 50% desired monobromide by TLC (SiO_2 -50% EtOAc in hexane).

Preparation of Compound (57) --

N-Methyl-4-(morpholinosulfonyl)benzylamine

To a 40% w/w aqueous methylamine solution (26.5 mL, 0.3 mol) in THF (10 mL) added to a solution of crude 4-(morpholino-sulfonyl)benzyl bromide (14 g) in THF (70 mL) during 15 min at 25°C. The amber-colored reaction mixture was poured into H_2O (500 mL) and extracted with CH_2Cl_2 (2 x 125 mL). The combined extracts were washed with H_2O (500 mL) and then shaken with 2N HCl (100 mL). The acid layer was washed with CH_2Cl_2 (50 mL), basified to pH 12 with 2N NaOH (100 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The extracts were combined, dried, and evaporated to give the technical grade product as an off-white waxy solid (3.43 g, 31% overall from N-(p-toluenesulfonyl)morpholine). Chromatography of a small portion on SiO_2 using 3% Et_3N in CH_3CN as eluant afforded the analytical sample, mp 92-93°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.26 (s, 3H, CH_3), 2.83 (m, 4H, morpholino), 3.62 (m, 4H, morpholino), 3.74 (s, 2H, CH_2), 7.60 (d, 2H, $J = 8.4$ Hz, aromatic), 7.67 (d, 2H, $J = 8.4$ Hz, aromatic), NH not visible. Anal. ($\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$) C, H, N, S.

Preparation of Compound (58) --

5-(N-(4-(Morpholinosulfonyl)benzyl)methylamino)
2-nitrobenzonitrile

A solution of N-methyl-4-(morpholinosulfonyl)benzylamine (3.35 g, 12.4 mmol) and 5-chloro-2-nitrobenzonitrile (2.49 g, 13.6 mmol, 1.1 eq) in DMSO (25 mL) with CaCO_3 (1.49 g, 14.9 mmol, 1.20 eq) in suspension was stirred at 105°C for 80 min. The mixture was filtered through celite, and the filtrate was poured into H_2O (350 mL) and extracted with EtOAc (100 mL). Brine (100 mL) was added to the aqueous layer which was extracted once more with EtOAc (75 mL). The combined extracts were dried and evaporated to give a solid residue which was shaken vigorously with warm EtOH (25 mL). The thus purified yellow product was filtered off and washed with cold

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EtOH (50 mL), (1.86 g, 37%), mp 201-203°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.83 (m, 4H, morpholino), 3.25 (s, 3H, CH_3), 3.62 (m, 4H, morpholino), 4.97 (s, 2H, CH_2), 7.06 (dd, 1H, $J = 3.0, 9.6$ Hz, H^4), 7.40 (d, 1H, $J = 3.0$ Hz, H^6), 7.46 (d, 2H, $J = 8.4$ Hz, aromatic), 7.72 (d, 2H, $J = 8.4$ Hz, aromatic), 8.18 (d, 1H, $J = 9.6$ Hz, H^3). Anal. ($\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_5\text{S}$) C, H, N, S.

Preparation of Compound (59) --

2-Amino-5-(N-(4-(morpholinosulfonyl)benzyl)
methylamino)benzonitrile

To a solution of 5-(N-(4-(morpholinosulfonyl)benzyl)-methylamino)-2-nitrobenzonitrile (1.80 g, 4.32 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (50 mL) with CuCl (1.28 g, 13 mmol, 3 eq) in suspension was added KBH_4 (1.63 g, 30.2 mmol, 7 eq) in one portion. The mixture was stirred at 25°C for 20 min, and the black copper salts were filtered off. The filtrate was washed with H_2O (400 mL), dried, and evaporated to give a brown residue which was chromatographed on SiO_2 (100 g) using 35% hexane in EtOAc as eluant to give the product as a yellow solid (0.54 g, 32%) mp 194-196°C. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.81-2.83 (m, 4H, morpholino), 2.83 (s, 3H, CH_3), 3.60-3.63 (m, 4H, morpholino), 4.51 (s, 2H, CH_2), 5.36 (s, 2H, NH_2), 6.71-6.74 (m, 2H, H^3 & H^6), 6.97 (dd, 1H, $J = 9.1, 2.9$ Hz, H^4), 7.46 (d, 2H, $J = 8.3$ Hz, aromatic), 7.68 (d, 2H, $J = 8.3$ Hz, aromatic), Anal. ($\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$) C, H, N, S.

Preparation of Compound (60) --

2,4-Diamino-6-(N-(4-(morpholinosulfonyl)
benzyl)methylamino)quinazoline

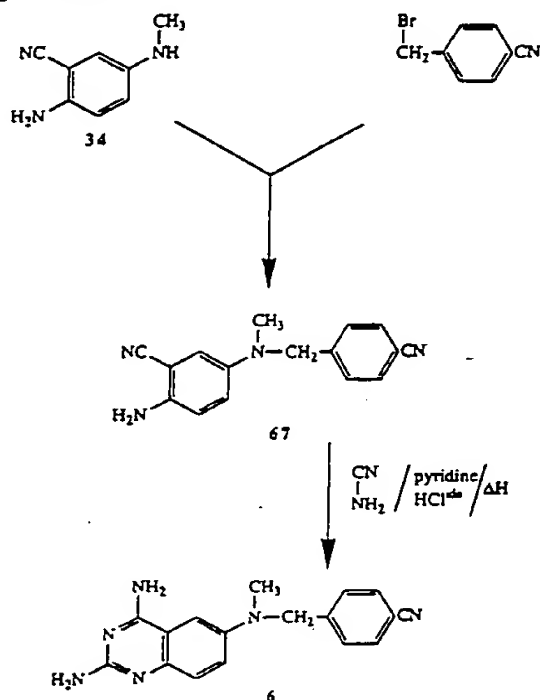
A solution of 2-amino-5-(N-(4-(morpholinosulfonyl)benzyl)methylamino)benzonitrile (0.54 g, 1.4 mmol) in diglyme (6 mL) was treated with chlorformamidine hydrochloride (0.19 g, 1.7 mmol, 1.2 eq), and the resulting mixture was heated at 130°C. At 1 h, further chlorformamidine hydrochloride (0.08 g, 0.7 mmol, 0.5 eq) was added. At 1 h 40 min, the mixture was cooled, and the diglyme layer was decanted from the brown resin which had formed. The resin was dissolved in DMF (4.5 mL), treated with Et_3N (0.97 mL, 7 mmol, 5 eq), poured into H_2O (50 mL),

and extracted with EtOAc (25 mL). Saturated brine (50 mL) was added to the aqueous layer and it was extracted once more with EtOAc (25 mL). The extracts were combined, dried, and evaporated to give an orange-colored oil which was chromatographed on basic alumina (38 g) using 6% MeOH in CH_2Cl_2 as eluant. The lemon-yellow solid obtained was washed with CH_2Cl_2 (10 mL) and filtered to give pure material (32 mg, 5.3%), mp 267°C dec. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.82 (m, 4H, morpholino), 2.95 (s, 3H, CH_3), 3.61 (m, 4H, morpholino), 4.68 (s, 2H, CH_2), 5.61 (s, 2H, NH_2), 7.08-7.22 (m, 5H, H^5 , H^7 , H^8 & NH_2), 7.50 (d, 2H, $J = 8.3$ Hz, aromatic), 7.68 (d, 2H, $J = 8.3$ Hz, aromatic). Anal. ($\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_3\text{S} \cdot 0.6 \text{H}_2\text{O}$) C, H, N, S. HRMS ($\text{C}_{20}\text{H}_{24}\text{N}_6\text{O}_3\text{S}$)⁺ calcd, 428.1631; found, 428.1628.

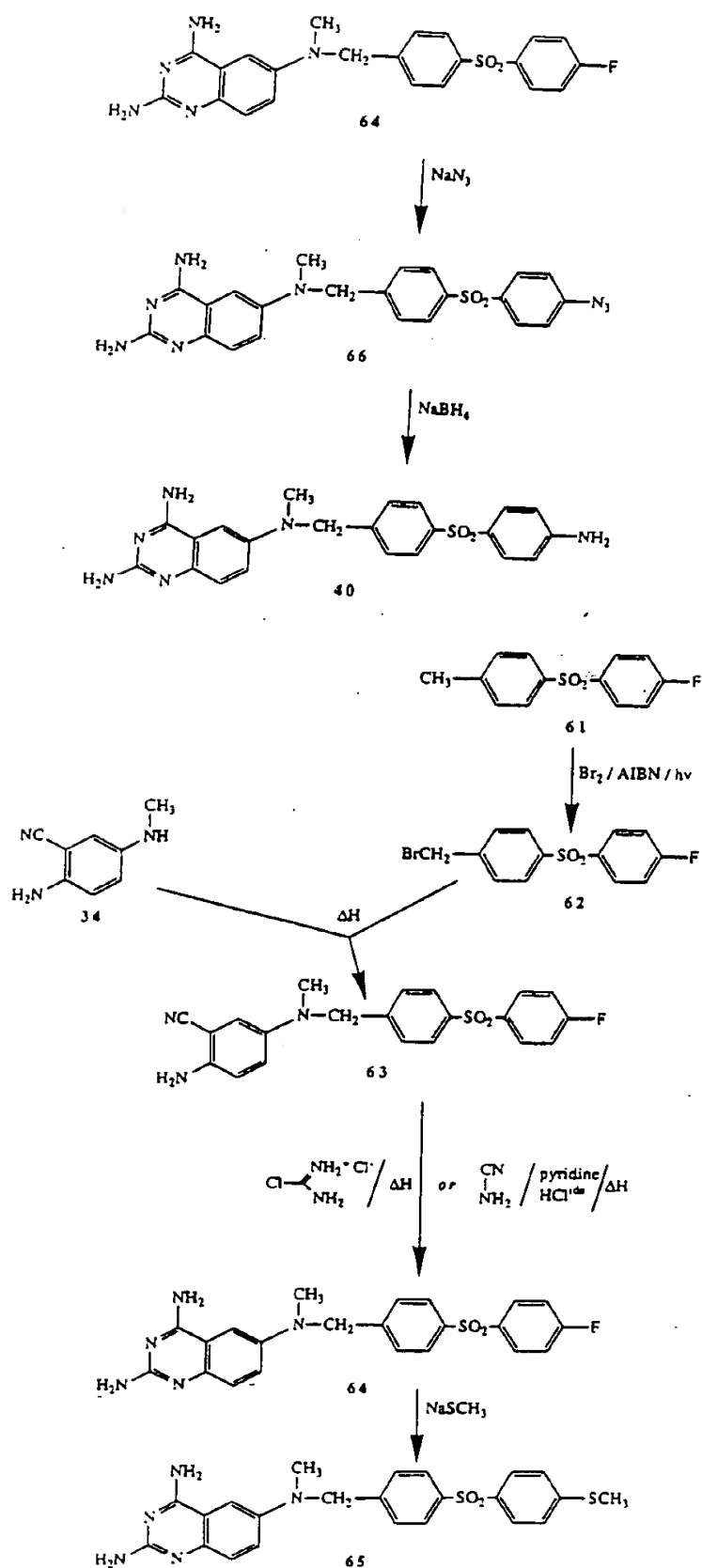
An alternative annelation process for preparing this compound using cyanamide as the reagent is described on page 124 and 125.

Example 9: Preparation of Compounds 64 and 65, and Alternate Methods for Preparing Compounds 6 and 40

Compounds 6, 40, 64 and 65 were prepared according to the following reaction scheme:



- 61 -



Preparation of Compound (62) --

4-((4-Fluorophenyl)sulfonyl)benzyl bromide

A solution of commercially available 4-fluorophenyl p-tolyl sulfone (61 50.06 g, 200 mmol) in C_6H_6 (240 mL) in contact with H_2O (80 mL) was stirred vigorously at reflux. A few granules of AIBN were added, and the mixture, irradiated with a 200 watt bulb, was treated dropwise with bromine (13.4 mL, 260 mmol, 1.3 eq) in C_6H_6 (80 mL) during 40 min. Heating of the colorless reaction mixture was discontinued, and the water layer was immediately removed by pipet. The organic phase was dried and concentrated to give a peach-colored oil which slowly solidified upon standing (72.4 g). NMR (Me_2SO-d_6) showed that this material was 88% desired product; the remainder was starting material (< 10%) and C_6H_6 . It was used without further purification.

Preparation of Compound (63) --

2-Amino-5-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)methylamino)benzonitrile

A solution of the crude 88% 4-((4-fluorophenyl)sulfonyl)-benzyl bromide (26.2 g., 70 mmol), 2-amino-5-(methylamino)-benzonitrile (13.64 g, 77 mmol, 1.1 eq) and N,N-diisopropylethylamine (13.4 mL, 77 mmol, 1.1 eq) in DMA (250 mL) was stirred at 75°C under argon for 2h 40 min. The mixture was poured into 20% saturated brine (2.5 L) and extracted with EtOAc (3 x 500 mL). The combined extracts were dried and evaporated to give a crude brown oil which was chromatographed twice on SiO_2 (500 g) using 30% EtOAc in hexane as eluant and once on SiO_2 (500 g) using a gradient of 40-45% EtOAc in hexane to give the technical grade product as an orange-colored solid (19.2 g, 69%). The analytical sample was prepared by chromatography on SiO_2 using 30% hexane in EtOAc, mp 46-48°C. NMR (Me_2SO-d_6) δ 2.80 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 5.34 (s, 2H, NH_2), 6.68-6.71 (m, 2H, H^3 & H^6), 6.93 (dd, 1H, J = 9.1, 3.0 Hz, H^4), 7.41 (d, 2H, J = 8.4 Hz, aromatic) 7.46 (d, 2H, J = 8.9 Hz, aromatic), 7.86 (d, 2H, J

= 8.2 Hz, aromatic), 8.02 (m, 2H, J = 8.9 Hz, $J_{F,H}$ = 5.1 Hz aromatic). Anal. ($C_{21}H_{18}FN_3O_2S$) C, H, N, S.

Preparation of Compound (64) --

2,4-Diamino-6-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)methylamino)quinazoline

Method A. A mixture of 2-amino-5-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)methylamino)benzonitrile (0.40 g, 1 mmol), chlorformamidinium hydrochloride (0.14 g, 1.2 mmol, 1.2 eq) in diglyme (5 mL) was stirred at 110°C for 50 min. When cool, the diglyme layer was decanted from the brown resin which had formed. The resin was dissolved in EtOH (30 mL), treated with N,N-diisopropylethylamine (0.69 mL, 4 mmol, 4 eq), poured into saturated brine (175 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were dried and coated onto basic alumina (2 g). Chromatography on basic alumina (40 g) with 10% MeOH in CH_2Cl_2 as eluant gave the product as an orange-colored solid (40 mg, 9.2%), mp 272-274°C. NMR (Me_2SO-d_6) δ 2.93 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 5.59 (s, 2H, NH_2), 7.05-7.16 (m, 5H, H^5 , H^7 , H^8 , & NH_2), 7.44 (d, 2H, J = 8.4 Hz, aromatic), 7.46 (d, 2H, J = 8.9 Hz, aromatic), 7.91 (d, 2H, J = 8.4 Hz, aromatic), 8.01 (m, 2H, J = 8.9 Hz, $J_{H,F}$ = 5.1 Hz, aromatic). Anal. ($C_{22}H_{20}FN_5O_2S \cdot 0.5 H_2O$) C, H, N, S. HRMS ($C_{22}H_{20}FN_5O_2S$)⁺ calcd, 437.1322; found, 437.1335.

The diglyme layer was poured into dilute brine (85 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were dried and evaporated to give an oil which was chromatographed on SiO_2 (50 g) with 50% EtOAc in hexane as eluant to give 4-((4-fluorophenyl)sulfonyl)benzaldehyde as a yellow solid (57 mg, 22%), mp 111-113°C - a by-product formed by benzylic cleavage. NMR (Me_2SO-d_6) δ 7.50 (m, 2H, aromatic), 8.08-8.21 (m, 6H, aromatic), 10.08 (s, 1H, CHO). Anal. ($C_{13}H_9FO_3S$) C, H, F, S.

Method B. A mixture of 2-amino-5-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)methylamino)benzonitrile (1.98 g, 5 mmol), pyridine hydrochloride (3.47 g, 30 mmol, 6 eq),

and cyanamide (0.84 g, 20 mmol, 4 eq), was heated at 165°C to give a brown melt which spontaneously resolidified after 5 min. The mixture was immediately cooled, and the solid was broken up and triturated with boiling EtOH (25 mL), treated give a brown melt which spontaneously resolidified after 5 min. The mixture was immediately cooled, and the solid was with Et₃N (5.6 mL, 40 mmol, 8 eq), shaken vigorously, filtered off, and washed with EtOH (2 x 12 mL) followed by Et₂O (2 x 6 mL) to give the yellow, technical quality product (1.22 g, 55%). Anal. (C₂₂H₂₀FN₅O₂S · 2H₂O) C, H, N, F, S.

Preparation of Compound (65) --

2,4-Diamino-6-(N-(4-((4-(methylthio)phenyl)
sulfonyl)benzyl)methylamino)quinazoline

A turbid mixture of 2,4-diamino-6-(N-(4-((4-(fluorophenyl) sulfonyl)benzyl)methylamino)quinazoline (1.01 g, 2.3 mmol) and NaSMe (0.40 g, 4.8 mmol, 2.5 eq) in DMSO (20 mL) was heated at 85°C for 2.5 h and then dripped into H₂O (200 mL) during 5 min to give the crude product as a yellow-orange solid which was filtered off, washed with H₂O (50 mL), and air dried. The product was dissolved in hot DMF (50 mL) and charcoal treated, and the resulting filtrate was diluted with H₂O to cloud point and let cool. The resulting solid was filtered off, washed with H₂O (3 x 50 mL) followed by MeOH (2 x 50 mL) and dried in a desiccator. TLC (10% MeOH in CH₂Cl₂) on basic alumina showed the product to contain faint impurities. The material (0.716 g) was therefore dissolved in DMF (10 mL), coated onto basic alumina (5 g), and chromatographed on Al₂O₃ (55 g) with 10% MeOH in CH₂Cl₂ to give the analytically pure product as a lemon-yellow solid (0.234 g, 22%), mp 252-254°C. NMR (Me₂SO-d₆) δ 2.55 (s, 3H, S-CH₃), 2.97 (s, 3H, N-CH₃), 4.67 (s, 2H, CH₂), 5.71 (s, 2H, NH₂), 7.11-7.21 (m, 5H, H³, H⁷, H⁸, & NH₂), 7.47 (m, 4H, aromatic), 7.86 (d, 2H, J = 8.6 Hz, aromatic), 7.92 (d, 2H, J = 8.4 Hz, aromatic). Anal. (C₂₃H₂₃N₅O₂S₂ · 0.8 H₂O)

-65-

C,H,N,S. HRMS, FAB: nitrobenzyl alcohol matrix,
(C₂₃H₂₄N₅O₂S₂)⁺ calcd, 466.1371; found, 466.1369.

Preparation of Compound (66) --

2,4-Diamino-6-(N-(4-((4-azidophenyl)sulfonyl)
benzyl)methylamino)quinazoline

NaN₃ (0.56 g, 8.58 mmol, 2.5 eq) was added to a solution of 2,4-diamino-6-(N-(4-((4-fluorophenyl)sulfonyl)benzyl)methylamino)quinazoline (64, 1.5 g, 3.43 mmol) in HMPA (40 mL), and the resulting mixture was stirred at 105°C under argon for 2 h. The turbid mixture was poured with vigorous stirring into H₂O (400 mL) which had been basified to pH 11 with 0.1 N NaOH. The resulting crude, yellow, flocculent, solid product was filtered off, washed with H₂O (50 mL), and dried over P₂O₅ in vacuo (1.23 g, 77.8%). Its NMR spectrum (Me₂SO-d₆) was satisfactory, and it was used without further purification.

Preparation of Compound (40) --

2,4-Diamino-6-(N-(4-((4-aminophenyl)sulfonyl)
benzyl)methylamino)quinazoline

To a partial suspension of crude 2,4-diamino-6-(N-(4-((4-azidophenyl)sulfonyl)benzyl)methylamino)quinazoline (1.15 g, 2.50 mmol) in n-BuOH (50 mL) was added NaBH₄ (0.14 g, 3.75 mmol, 1.5 eq), and the resulting mixture was heated under reflux for 25 min. The mixture was removed from heat, treated with MeOH (50 mL), and cooled in ice for 15 min. The crude solid product was filtered off and washed with MeOH (30 mL). The filtrate was poured into H₂O (500 mL) and extracted with EtOAc (300 mL). The extract was dried and evaporated to give a residue which, combined with the product obtained by filtration, was dissolved in DMSO (20 mL) and coated onto basic alumina (8 g). Chromatography on alumina (100 g) using 8% MeOH in CH₂Cl₂ as eluant gave the pure product as a pale yellow solid (159 mg). The column was washed with MeOH (100 mL), and the effluent was evaporated to dryness to give a residue which was coated onto alumina from DMF (0.5 mL).

Rechromatography on basic alumina (80 g) using the same eluant gave additional pure product (40 mg); total yield 18.2%. NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory.

Preparation of Compound (67) --

2-Amino-5-(N-(4-cyanobenzyl)
methylamino)benzonitrile

A solution of 2-amino-5-(methylamino)benzonitrile (34, 2.43 g, 16.5 mmol), α -bromo-p-tolunitrile (2.94 g, 15 mmol) and N, N-diisopropylethylamine (5.2 mL, 30 mmol) in DMA (20 mL) was stirred at 70°C for 50 min. The cooled mixture was poured into H_2O (500 mL) and extracted with EtOAc (2 x 150 mL). The combined extracts were dried and evaporated to give a residue that was chromatographed on SiO_2 (100 g) with 45% EtOAc in hexane to give the crude oily product (3.65 g) which was rechromatographed on SiO_2 (150 g) using 50% EtOAc in hexane to give a technical grade product as a brown viscous oil (2.55 g, 65%). An analytical sample was prepared by chromatography of a small portion on SiO_2 using 50% EtOAc in petrol to give a light amber oil. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.83 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 5.35 (s, 2H, NH_2), 6.69-6.70 (m, 2H, H^3 , H^6), 6.96 (dd, 1H, $J = 9.1, 3.0$ Hz, H^4), 7.38 (d, 2H, $J = 8.3$ Hz, aromatic), 7.78 (d, 2H, $J = 8.3$ Hz, aromatic). Anal. ($\text{C}_{16}\text{H}_{14}\text{N}_4$) C, H, N.

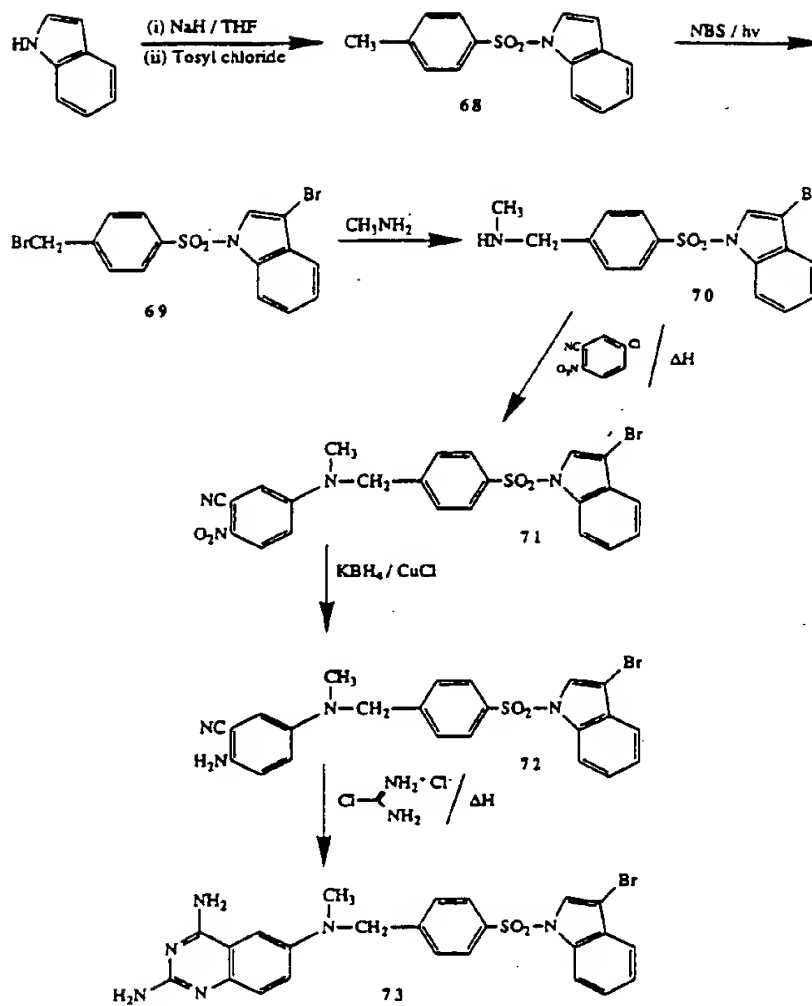
Preparation of Compound (6) --

2,4-Diamino-6-(N-(4-cyanobenzyl)
methylamino)quinazoline

The annelation of compound (67) with cyanamide to provide the title compound is described on page 124.

Example 10: Preparation of Compound 73

Compound 73 was prepared according to the following reaction scheme:



Preparation of Compound (68) --

1-(4-Methylphenylsulfonyl)indole

A solution of indole (11.72 g, 0.10 mol) in THF (70 mL) was added under Ar to a slurry of 60% NaH (4.40 g, 0.11 mol) in THF (40 mL) at 0°C. This mixture was stirred at ambient temperature for 90 min, then cooled to 0°C prior to the addition of a solution of p-toluenesulfonyl chloride (20.97 g, 0.11 mol) in THF (100 mL) during 40 min. The resultant mixture was stirred at ambient temperature for 3 h, then poured into H₂O (200 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were dried and evaporated to give a solid which was recrystallized from hexane to afford the product as an off-white solid (25.09 g, 92%), mp 84-86°C, NMR (CDCl₃) δ 2.32 (s, 3H, CH₃) 6.65 (d, 1H, J = 3.7 Hz, H³), 7.21 (d, 2H, J = 8.4 Hz, aromatic) 7.24-7.33 (m, 2H, H⁵ & H⁶), 7.53 (d, 1H, J = 7.7 Hz, H⁴), 7.57 (d, 1H, J = 3.7 Hz, H²), 7.77 (d, 2H, J = 8.4 Hz, aromatic) 8.00 (d, 1H, J = 8.3 Hz, H⁷). Anal. (C₁₅H₁₃NO₂S) C, H, N, S.

Preparation of Compound (69) --

4-((3-Bromo-1-indolyl)sulfonyl)benzyl bromide

N-Bromosuccinimide (7.65 g, 43 mmol) was added to a solution of 68 (5.43 g, 20 mmol) in CCl₄ (100 mL). This mixture was heated to reflux and irradiated with an external light source (200 watt, 120 volt) for 4 h. The cooled reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give an orange-colored gum (7.0 g) suitable for further use. Chromatographic purification of a small portion (SiO₂/10% EtOAc in hexane) provided the analytical sample as a yellow solid, mp 132-133°C, NMR (CDCl₃) δ 4.39 (s, 2H, CH₂), 7.30-7.42 (m, 2H, H⁵ & H⁶), 7.47 (d, 2H, J = 8.5 Hz, aromatic), 7.51 (dd, 1H, J = 7.3, 1.2 Hz, H⁴), 7.61 (s, 1H, H³), 7.86 (d, 2H, J = 8.5 Hz, aromatic), 7.99 (d, 1H, J = 8.0 Hz, H⁷). Anal. (C₁₅H₁₁Br₂NO₂S) C, H, N, Br, S.

Preparation of Compound (70) --

N-Methyl-4-((3-bromo-1-indolyl)sulfonyl)benzylamine

A solution of crude 69 (7.0 g) in THF (60 mL) was added to a mixture of 40% w/w aqueous CH_3NH_2 (25 mL, 0.29 mol) and THF (25 mL) during 30 min at 25°C. The mixture was acidified with 6 N HCl, and the layers were separated. The organic phase was evaporated to give a residue which was partitioned between 2N HCl (100 mL) and CH_2Cl_2 (100 mL). The combined acidic aqueous extracts were made alkaline with 15% NaOH, then extracted with Et_2O (3 x 100 mL). The combined ether extracts were dried and evaporated to give a yellow gum which was purified by flash chromatography. Elution with ether containing increasing amounts of methanol up to 25% provided the product as a yellow oil (2.59 g, 34%), NMR (CDCl_3) δ 2.39 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 7.28-7.37 (m, 2H, H^5 & H^6), 7.41 (d, 2H, $J = 8.4$ Hz, aromatic), 7.49 (d, 1H, $J = 7.6$ Hz, H^4), 7.62 (s, 1H, H^2), 7.84 (d, 2H, $J = 8.4$ Hz, aromatic), 7.99 (d, 1H, $J = 8.3$ Hz, H^7). Anal. ($\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_2\text{S}$) C, H, N, Br, S.

Preparation of Compound (71) --

5-(N-(4-((3-Bromo-1-indolyl)sulfonyl)benzyl)methylamino)-2-nitrobenzonitrile

A mixture of 70 (2.59 g, 6.8 mmol), 5-chloro-2-nitrobenzonitrile (1.25 g, 6.9 mmol) and CaCO_3 (1.37 g, 13.7 mmol) in DMSO (30 mL) was heated at 100°C for 16 h. The mixture was cooled and filtered, and the filtrate was concentrated *in vacuo*. A solution of the resulting gum in CHCl_3 (150 mL) was washed with H_2O (3 x 100 mL), dried and concentrated, *in vacuo*, to give a yellow oil which was purified by flash chromatography. Elution with 50% EtOAc in hexane afforded the product as a yellow solid (2.07 g, 58%), mp 206-208°C, NMR (CDCl_3) δ 3.18 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 6.73 (dd, 1H, $J = 9.5, 2.9$ Hz, H^4), 6.94 (d, 1H, $J = 2.9$ Hz, H^6), 7.23 (d, 2H, $J = 8.3$ Hz, aromatic), 7.33-7.41 (m, 2H, H^5 & H^6), 7.51 (dd, 1H, $J = 7.3, 1.2$ Hz, H^4), 7.60 (s, 1H, H^2), 7.89 (d, 2H, $J = 8.3$ Hz, aromatic), 7.98 (d, 1H, $J = 8.0$ Hz,

iH^7), 8.15 (d, 1H, $J = 9.5$ Hz, H^3). Anal. ($C_{23}H_{17}BrN_4O_4S$) C, H, N, Br, S.

Preparation of Compound (72) --

2-Amino-5-(N-(4-((3-Bromo-1-indolyl)sulfonyl)benzyl)methylamino)benzonitrile

To a mixture of 71 (2.22 g, 4.2 mmol), CuCl (1.25 g, 12.6 mmol), CH_2Cl_2 (100 mL) and MeOH (50 mL) was added solid KBH_4 (1.59 g, 29.5 mmol) in 4 equal portions during 5 min. The resultant mixture was stirred for 90 min at 25°C, then filtered through a pad of celite. The filtrate was concentrated, *in vacuo*, to give a yellow solid which was purified by flash chromatography. Elution with 40% EtOAc in hexane afforded the product as a yellow solid (1.27 g, 61%), mp 96-99°C, NMR ($CDCl_3$) δ 2.84 (s, 3H, CH_3), 3.98 (s, 2H, NH_2), 4.35 (s, 2H, CH_2), 6.64 (d, 1H, $J = 8.9$ Hz, H^3), 6.66 (d, 1H, $J = 2.9$ Hz, H^5), 6.75 (dd, 1H, $J = 8.9, 2.9$ Hz, H^4), 7.29 (d, 2H, $J = 8.4$ Hz, aromatic), 7.32-7.41 (m, 2H, iH^5 & iH^6), 7.51 (d, 1H, $J = 7.3$ Hz, iH^4), 7.61 (s, 1H, iH^2), 7.84 (d, 2H, $J = 8.4$ Hz, aromatic), 7.99 (d, 1H, $J = 8.1$ Hz, iH^7). Anal. ($C_{23}H_{19}BrN_4O_2S$) C, H, N, Br, S.

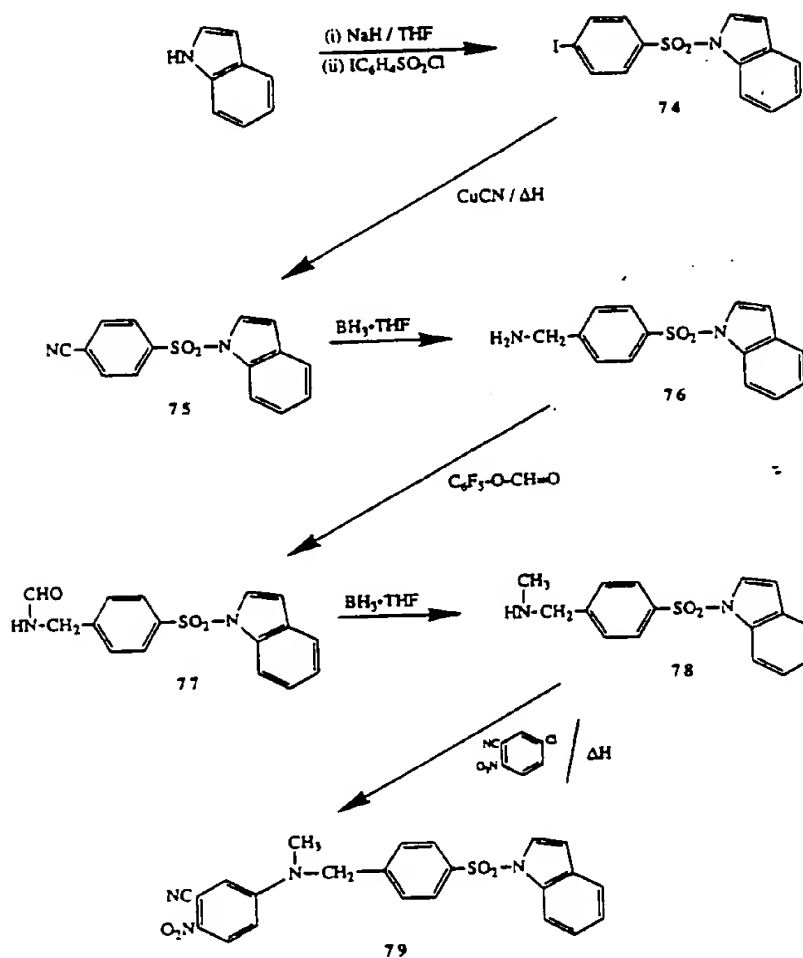
Preparation of Compound (73) --

2,4-Diamino-6-(N-(4-((3-bromo-1-indolyl)sulfonyl)benzyl)methylamino)quinazoline

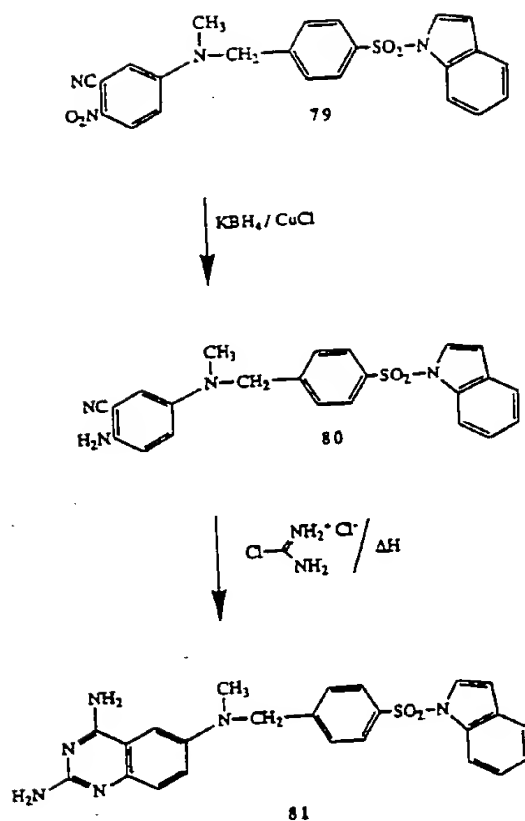
A mixture of 72 (1.39 g, 2.8 mmol) and chlorformamidine hydrochloride (0.36 g, 3.1 mmol) in bis (2-methoxyethyl) ether (5 mL) was heated at 140°C for 1h. The cooled mixture was diluted with ether (30 mL) and filtered to give a yellow solid. Recrystallization from EtOH, containing excess Et_3N , provided the product as a yellow powder (0.53 g, 35%), mp 255-257°C, NMR (Me_2SO-d_6) δ 2.92 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 6.47 (br s, 2H, NH_2), 7.14-7.20 (m, 3H, H^5 , H^7 , & H^8), 7.40 (d, 2H, $J = 8.4$ Hz, aromatic) 7.34-7.48 (m, 3H, iH^4 , iH^5 , & iH^6), 7.80 (br s, 2H, NH_2), 7.98 (d, 1H, $J = 8.1$ Hz, iH^7), 8.00 (d, 2H, $J = 8.4$ Hz, aromatic), 8.12 (s, 1H, iH^2). Anal. ($C_{24}H_{21}BrN_6O_2S \cdot 0.6H_2O \cdot 0.4HCl$) C, H, N, S. HRMS ($C_{24}H_{21}BrN_6O_2S$)⁺ calcd, 536.0630; found, 536.0610.

Example 11: Preparation of Compound 81

Compound 81 was prepared according to the following reaction scheme:



-72-



**Preparation of Compound (74) --
1-(4-Iodophenylsulfonyl)indole**

A solution of indole (4.68 g, 40 mmol) in THF (50 mL) was added under Ar to a slurry of 60% NaH (1.76 g, 44 mmol) in THF (25 mL) at 0°C. This mixture was stirred at ambient temperature for 1 h, then cooled to 0°C prior to addition of a solution of 4-iodophenylsulfonyl chloride (13.61 g, 45 mmol) in THF (50 mL). The resultant reaction mixture was stirred at ambient temperature for 15 h, then poured into H₂O (200 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were dried and concentrated, *in vacuo*, to give a solid which was recrystallized from EtOH to afford the product as tan needles (14.06 g, 92%), mp 126°C, NMR (CDCl₃) δ 6.68 (d, 1H, J = 3.4 Hz, H³), 7.21-7.27 (m, 1H, H⁵), 7.29-7.35 (m, 1H, H⁶), 7.52 (d, 1H, J = 3.4 Hz, H²), 7.54 (d, 1H, J = 6.4 Hz, H⁴), 7.57 (d, 2H, J = 8.6 Hz, aromatic), 7.78 d,

2H, $J = 8.6$ Hz, aromatic), 7.96 (d, 1H, $J = 8.3$ Hz, H^7).

Anal. ($C_{14}H_{10}INO_2S$) C, H, N, I, S.

Preparation of Compound (75) --

1-(4-Cyanophenylsulfonyl)indole

A mixture of 74 (7.66 g, 20 mmol) and CuCN (7.16 g, 80 mmol) in DMF (90 mL) was heated at 120°C for 4.5 h. The cooled reaction mixture was filtered through a pad of celite and the filtrate was concentrated, *in vacuo*, to give a dark green oil which was purified by flash chromatography.

Elution with 20% EtOAc in hexane provided the product as a white solid (5.11 g, 90%), mp 131-133°C, NMR (CD_3COCD_3) δ 6.86 (d, 1H, $J = 3.7$ Hz, H^3), 7.24-7.29 (m, 1H, H^5), 7.33-7.39 (m, 1H, H^6), 7.61 (d, 1H, $J = 7.7$ Hz, H^4), 7.73 (d, 1H, $J = 3.7$ Hz, H^2), 7.99 (d, 2H, $J = 8.6$ Hz, aromatic), 8.02 (d, 1H, $J = 7.4$ Hz, H^7), 8.19 (d, 2H, $J = 8.6$ Hz, aromatic).

Anal. ($C_{15}H_{10}N_2O_2S$) C, H, N, S.

Preparation of Compound (76) --

4-((1-Indolyl)sulfonyl)benzylamine

To a solution of 75 (4.23 g, 15 mmol) in THF (40 mL) was added 1.0 M BH_3 .THF (17 mL, 17 mmol) under Ar at 25°C. The resultant solution was heated under reflux for 4 h. The cooled mixture was diluted with 1.2 M methanolic HCl (15 mL), then heated under reflux for 3 h. The solvent was removed *in vacuo*, and the residue partitioned between 2M K_2CO_3 (75 mL) and ether (75 mL). The layers were separated and the aqueous phase further extracted with ether (75 mL). The combined extracts were dried and concentrated, *in vacuo*, to give an oil which was purified by flash chromatography. Elution with ether containing increasing amounts of methanol up to 25% provided the product as a yellow, waxy, crystalline solid (2.83 g, 66%), mp 93-94°C, NMR ($CDCl_3$) δ 3.86 (s, 2H, CH_2), 6.65 (d, 1H, $J = 3.6$ Hz, H^3), 7.19-7.24 (m, 1H, H^5), 7.28-7.33 (m, 1H, H^6), 7.38 (d, 2H, $J = 8.4$ Hz, aromatic), 7.52 (d, 1H, $J = 7.7$ Hz, H^4), 7.56 (d, 1H, $J = 3.6$ Hz, H^2), 7.84 (d, 2H, $J = 8.4$ Hz, aromatic), 7.99 (d, 1H, $J = 8.2$ Hz, H^7).
Anal. ($C_{15}H_{14}N_2O_2S$) C, H, N, S.

Preparation of Compound (77) --

N-Formyl-4-((1-indolyl)sulfonyl)benzylamine

A solution of pentafluorophenyl formate (2.97 g, 14 mmol) in CHCl_3 (25 mL) was added to a solution of 76 (2.00 g, 7 mmol) in CHCl_3 (50 mL). The resultant yellow solution was stirred at 25°C for 30 min. The CHCl_3 was removed *in vacuo*, and the residual orange-colored oil was purified by flash chromatography. Elution with 25% EtOAc in hexane afforded the product as a yellow solid (1.86 g, 85%), mp 156-158°C, NMR (CD_3COCD_3) δ 4.44 (d, 2H, $J = 6.2$ Hz, CH_2), 6.78 (d, 1H, $J = 3.7$ Hz, H^3), 7.20-7.25 (m, 1H, H^5), 7.30-7.36 (m, 1H, H^6), 7.48 (d, 2H, $J = 8.5$ Hz, aromatic), 7.58 (d, 1H, $J = 7.8$ Hz, H^4), 7.70 (d, 1H, $J = 3.7$ Hz, H^2), 7.97 (d, 2H, $J = 8.5$ Hz, aromatic), 8.01 (dd, 1H, $J = 8.4, 0.5$ Hz, H^7) 8.21 (s, 1H, CHO), NH not visible. Anal. ($\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$) C, H, N, S.

Preparation of Compound (78) --

N-Methyl-4-((1-indolyl)sulfonyl)benzylamine

To a solution of 77 (1.73 g, 5.5 mmol) in THF (35 mL) was added 1.0 M BH_3 .THF (12 mL, 12 mmol) under Ar at 25°C. The resultant solution was heated under reflux for 3 h. The cooled mixture was diluted with 1.4M methanolic HCl, then heated under reflux for 2.5 h. The solvent was removed *in vacuo*, and the residue partitioned between 2M K_2CO_3 (75 mL) and ether (50 mL). The layers were separated, and the aqueous phase further extracted with EtOAc (2 x 50 mL). The combined extracts were dried and concentrated, *in vacuo*, to give an oil which was purified by flash chromatography. Elution with CH_2Cl_2 containing increasing amounts of methanol up to 5% provided the product as a yellow oil (1.29 g, 78%), NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.18 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 6.83 (d, 1H, $J = 3.7$ Hz, H^3), 7.20-7.25 (m, 1H, H^5), 7.29-7.35 (m, 1H, H^6), 7.50 (d, 2H, $J = 8.4$ Hz, aromatic), 7.59 (d, 1H, $J = 7.8$ Hz, H^4), 7.79 (d, 1H, $J = 3.7$ Hz, H^2), 7.91 (d, 2H, $J = 8.4$ Hz, aromatic), 7.93 (d, 1H, $J = 7.5$ Hz, H^7), NH not visible. Anal. ($\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S} \cdot 0.5\text{H}_2\text{O}$) C, H, N, S.

Preparation of Compound (79) --
5-(N-(4-((1-Indolyl)sulfonyl)benzyl)
methylamino)-2-nitrobenzonitrile

A mixture of 78 (4.97 g, 16.5 mmol), 5-chloro-2-nitrobenzonitrile (2.92 g, 16.0 mmol) and CaCO_3 (3.31 g, 33.1 mmol) in DMSO (70 mL) was heated at 100°C for 15 h. The cooled mixture was filtered through a pad of celite, and the filtrate was concentrated, *in vacuo*, to give an oil which was purified by flash chromatography. Elution with 50% EtOAc in hexane provided the product as a yellow solid (1.27 g, 18%), mp 87-89°C, NMR (CD_3COCD_3) δ 3.31 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 6.80 (d, 1H, $J = 3.7$ Hz, iH^3), 7.03 (dd, 1H, $J = 9.5$, 3.0 Hz, H^4), 7.25 (d, 1H, $J = 3.0$ Hz, H^6), 7.22-7.27 (m, 1H, iH^5), 7.30-7.36 (m, 1H, iH^6), 7.44 (d, 2H, $J = 8.4$ Hz, aromatic), 7.60 (d, 1H, $J = 7.7$ Hz, iH^4), 7.70 (d, 1H, $J = 3.7$ Hz, iH^2), 7.97 (d, 2H, $J = 8.4$ Hz, aromatic), 8.01 (d, 1H, $J = 8.6$ Hz, iH^7), 8.14 (d, 1H, $J = 9.5$ Hz, H^3). Anal. ($\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_4\text{S}$) C, H, N, S.

Preparation of Compound (80) --
2-Amino-5-(N-(4-((1-indolyl)sulfonyl)benzyl)
methylamino)benzonitrile

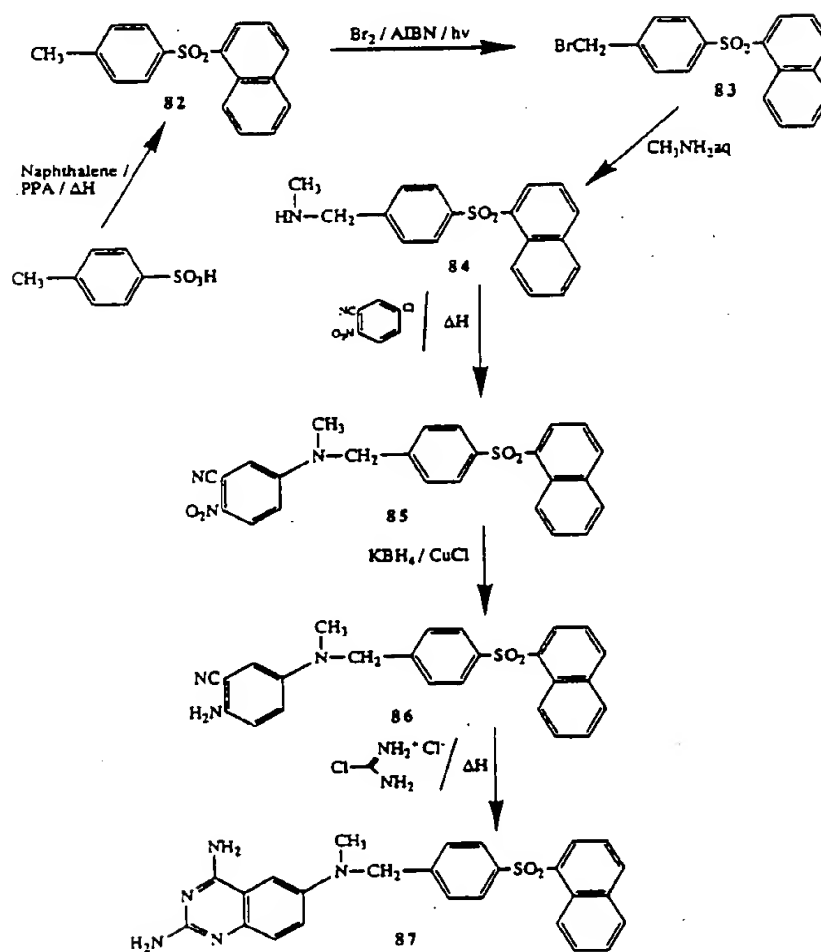
A mixture of 79 (1.24 g, 2.8 mmol), CuCl (0.83 g, 8.4 mmol), KBH_4 (1.05 g, 19.5 mmol), CH_2Cl_2 (15 mL), and CH_3OH (15 mL) was stirred at 25°C for 18 h, then filtered through a pad of celite. The filtrate was concentrated, *in vacuo*, and the residue obtained was purified by flash chromatography. Elution with 40% EtOAc in hexane afforded the product as a yellow solid (0.78 g, 67%), mp 125-126°C, NMR (CD_3COCD_3) δ 2.85 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 4.87 (br s, 2H, NH_2), 6.72 (d, 1H, $J = 3.0$ Hz, H^6), 6.76 (d, 1H, $J = 9.0$ Hz, H^3), 6.78 (d, 1H, $J = 3.7$ Hz, iH^3), 6.90 (dd, 1H, $J = 9.0$, 3.0 Hz, H^4), 7.21-7.26 (m, 1H, iH^5), 7.30-7.35 (m, 1H, iH^6), 7.42 (d, 2H, $J = 8.4$ Hz, aromatic), 7.58 (d, 1H, $J = 7.7$ Hz, iH^4), 7.70 (d, 1H, $J = 3.7$ Hz, iH^2), 7.93 (d, 2H, $J = 8.4$ Hz, aromatic), 8.01 (d, 1H, $J = 8.3$ Hz, iH^7). Anal. ($\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$) C, H, N, S.

Preparation of Compound (81) --
2,4-Diamino-6-(N-(4-((1-indolyl)sulfonyl)
benzyl)methylamino)quinazoline

A mixture of 80 (864 mg, 2.07 mmol) and chlorformamidine hydrochloride (264 mg, 2.30 mmol) in bis(2-methoxyethyl)ether (5 mL) was heated at 140°C for 1 h. The cooled reaction mixture was diluted with ether (35 mL), and the supernatant was decanted. The residue was dissolved, with heating, in a mixture of DMF (15 mL) and Et₃N (3 mL). This solution was poured into a mixture of ice (80 g) and 1 N NaOH (6 mL), then diluted with H₂O (70 mL). The resulting precipitate was collected by filtration and triturated with hexane-EtOAc to afford the product as a yellow solid (543 mg, 57%, mp 140-142°C dec, NMR (CD₃COCD₃) δ 2.92 (s, 3H, CH₃), 4.60 (s, 2H, CH₂), 5.07 (br s, 2H, NH₂), 6.46 (br s, 2H, NH₂), 6.78 (d, 1H, J = 3.7 Hz, iH³), 7.13 (d, 1H, J = 2.0 Hz, H⁵), 7.16-7.18 (m, 2H, H⁷ & H⁸), 7.20-7.25 (m, 1H, iH⁵), 7.29-7.35 (m, 1H, iH⁶), 7.44 (d, 2H, J = 8.4 Hz, aromatic), 7.59 (d, 1H, J = 7.8 Hz, iH⁴), 7.70 (d, 1H, J = 3.7 Hz, iH²), 7.94 (d, 2H, J = 8.4 Hz, aromatic), 8.01 (d, 1H, J = 8.3 Hz, iH⁷). Anal. (C₂₄H₂₂N₆O₂S) C, H, N, S. HRMS (C₂₄H₂₂N₆O₂S)⁺ calcd, 458.1525; found, 458.1505.

Example 12: Preparation of Compound 87

Compound 87 was prepared according to the following reaction scheme:



Preparation of Compound (82) --

4-((1-Naphthyl)sulfonyl)toluene

4-((1-Naphthyl)sulfonyl)toluene (82) was prepared by the method of B. Graybill [*J. Org. Chem.* 32, 2931, (1967)]: Naphthalene (33.6 g, 0.26 mol), p-toluenesulfonic acid (40.2 g, 0.21 mol) and polyphosphoric acid (600 g) were placed in a flanged reaction kettle with mechanical stirring and heated at 80°C for 8 h. The mixture was removed from the heat and poured into ice-water (1200 mL). The resulting white precipitate was filtered off and recrystallized from EtOH (250 mL) to give the product as white microneedles (49.0 g, 67%). An analytical sample was prepared by recrystallization twice from EtOH, mp 121-123°C, [Lit: H. Meyer, *Justus Liebig's Annalen der Chemie*, 433 327 (1923) quotes 122°C], NMR satisfactory, Anal. ($C_{17}H_{14}O_2S$) C, H, S.

Preparation of Compound (83) --

4-((1-Naphthyl)sulfonyl)benzyl bromide

4-((1-Naphthyl)sulfonyl)toluene (49.0 g, 0.174 mol) was dissolved in warm benzene (250 mL). H_2O (100 mL) was then added, and the mixture brought to reflux. A few grains of AIBN were added to the mixture, and a 200 watt light was shone on it. A solution of bromine (9.8 mL, 0.19 mol, 1.1 eq.) in benzene (100 mL) was then added dropwise during 40 min at a rate that maintained an orange-red color. The organic layer was separated, dried, and evaporated to give a white solid (63.0 g) which was used without further purification.

Preparation of Compound (84) --

N-Methyl-4-((1-naphthyl)sulfonyl)benzylamine
hydrobromide

Crude 4-((1-naphthyl)sulfonyl)benzyl bromide (63.0 g, <0.17 mol) dissolved in THF (300 mL) was added dropwise during 2 h to a stirred solution of 40% w/w aqueous methylamine (300 mL, 3.4 mol, 20 eq) in THF (300 mL). The mixture was then evaporated to dryness, and the resulting solid was adsorbed onto SiO_2 from DMF and chromatographed on SiO_2 (3.5 in x 7 cm od). Elution first with EtOAc removed

unbrominated 82; MeOH then eluted the product. The appropriate fractions were evaporated to give a thick paste which was taken up in cold EtOH. Addition of Et₂O precipitated the yellow solid product which was collected, and dried (25.8 g, 37.4% from 82), mp 198-201°C, NMR (Me₂SO-d₆) δ 2.52 (s, 3H, CH₃), 4.16 (s, 2H, CH₂), 7.65 (m, 4H, aromatic), 7.79 (t, 1H, J = 7.9 Hz, aromatic), 8.08 (m, 3H, J = 8.6 Hz, aromatic), 8.35 (d, 1H, J = 8.2 Hz, aromatic), 8.50 (d, 2H, J = 7.5 Hz, aromatic), 8.79 (s, 1H, NH). Anal. (C₁₈H₁₈BrNO₂S · 0.3H₂O) C, H, N, S; Br: calcd, 20.09; found, 23.02, 23.11.

Preparation of Compound (85)

5-(N-(4-((1-naphthyl)sulfonyl)benzyl) methyamino)-2-nitrobenzonitrile

A solution of N-methyl-4-((1-naphthyl)sulfonyl)benzylamine hydrobromide (12.1 g, 0.03 mol), 5-chloro-2-nitrobenzonitrile (5.5 g, 0.03 mol), and N,N-diisopropylethylamine (7.95 mL, 0.045 mol, 1.5 eq.) in DMSO (10.3 mL) was heated at 110°C for 1 h. The mixture was then poured into one third-saturated brine (300 mL), and the resulting yellow precipitate was filtered off, washed with H₂O (500 mL) followed by diethyl ether (200 mL), and dried in vacuo over P₂O₅ to provide the technical grade product (12.4 g 89%). An analytical sample was prepared by a first flash chromatography on silica using 70% EtOAc in hexane, a second chromatography using 60% EtOAc in hexane, and finally recrystallization from CH₃CN to give yellow microneedles, mp 243.5-245.5°C, NMR (Me₂SO-d₆) δ 3.16 (s, 3H, CH₃), 4.87 (s, 2H, CH₂), 6.96 (dd, 1H, J = 2.8, 9.5 Hz, H⁴), 7.31 (d, 1H, J = 2.8 Hz, H⁶), 7.36 (d, 2H, J = 8.3 Hz, aromatic), 7.64 (m, 2H, np), 7.76 (t, 1H, np), 7.96 (d, 2H, J = 8.3 Hz, aromatic), 8.10 (d, 2H, J = 9.5 Hz, H³ plus np), 8.32 (d, 1H, J = 8.3 Hz, np), 8.46 (d, 1H, J = 7.2 Hz, np), 8.52 (d, 1H, J = 8.2 Hz, np). Anal. (C₂₅H₁₉N₃O₄S) C, H, N, S.

Preparation of Compound (86) --
2-Amino-5-(N-(4-((1-naphthyl)sulfonyl)benzyl)methylamino)benzonitrile

KBH_4 (32.3 g, 0.59 mol, 7 eq) was added during 1 h to a stirred slurry of 5-(N-(4-((1-naphthyl)sulfonyl)benzyl)methylamino)-2-nitrobenzonitrile (39.1 g, 0.08 mol) in a mixture of CH_2Cl_2 (1600 mL), and MeOH (1600 mL) containing CuCl (25.4 g, 0.25 mol, 3 eq) in suspension. The black mixture was stirred at 25°C for 2h. It was then filtered, and the filtrate was divided into 3 equal portions. Each portion was extracted with H_2O (1 L) and the organic layer was removed. These were recombined and split into two portions, each of which was washed with brine (1 L). The combined organic layers were dried, and evaporated to give a brown foam. This was dissolved in EtOAc, and the solution was filtered through celite. The filtrate was evaporated to give a rust-colored solid (23.3 g, 64%). Preparative TLC of a small portion using first 20% EtOAc in hexane, followed by CH_3CN , as eluants gave an analytical sample as an amorphous gold-colored solid, mp > 50°C dec. NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.77 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 5.35 (br s, 2H, NH_2), 6.69 (m, 2H, H^6 , H^3), 6.90 (dd, 1H, $J = 2.8, 9.1$ Hz, H^4), 7.39 (d, 2H, $J = 8.2$ Hz, aromatic), 7.65 (m, 2H, np), 7.78 (t, 1H, $J = 7.8$ Hz, np), 7.94 (d, 2H, $J = 8.2$ Hz, aromatic), 8.10 (d, 1H, $J = 7.7$ Hz, np), 8.33 (d, 1H, $J = 8.2$ Hz, np), 8.48 (d, 1H, $J = 7.3$ Hz, np), 8.54 (d, 1H, $J = 8.2$ Hz, np). Anal. ($\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$) C, H, N, S.

Preparation of Compound (87) --
2,4-Diamino-6-(N-(4-((1-naphthyl)sulfonyl)benzyl)methylamino)quinazoline

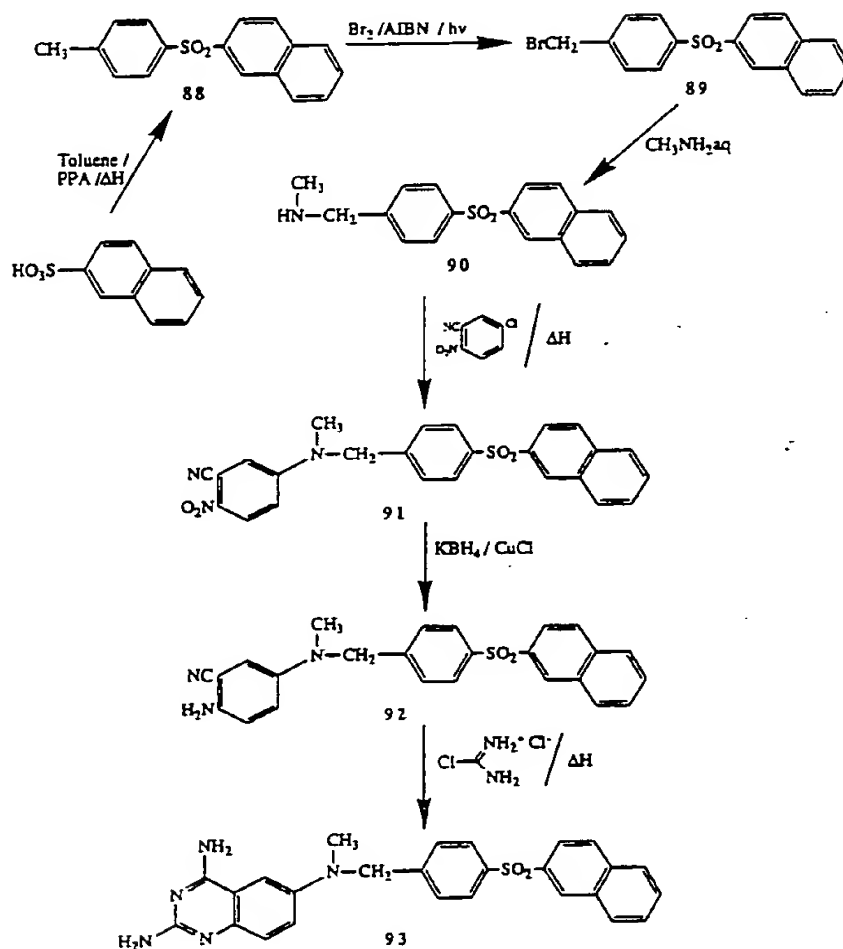
2-Amino-5-(N-(4-((1-naphthyl)sulfonyl)benzyl)methylamino)benzonitrile (23.3 g, 54.6 mmol) and diglyme (100 mL) were stirred at about 70°C for 20 min. Chlorformamidine hydrochloride (7.5 g, 65.5 mmol, 1.2 eq) was then added in portions during 15 min. The resulting mixture was heated at 150°C for 1.5 h with occasional manual stirring with a glass rod. The cooled mixture was triturated with Et_2O (2 x 100

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mL). The ether was decanted, and the remaining solid was dissolved in a warm water mixture of DMF (260 mL) and Et₃N (26 mL). The resulting solution was treated with charcoal and filtered. The filtrate was poured onto a mixture of ice (1 Kg) and 10% NaOH (260 mL) and stirred until the ice melted. The resulting yellow precipitate was filtered off and washed with H₂O and then Et₂O. It was adsorbed onto gravity silica from DMF and loaded onto a 13 cm OD column packed with 5 in of SiO₂. The column was eluted with 4% Et₃N/8% MeOH/88% CH₂Cl₂. The best fractions were evaporated to give the product as a bright yellow solid (0.49 g, 2%), mp > 190°C dec. A second chromatography of material from impure fractions yielded further pure product (4.9 g, 19%), and some impure product (3.0 g). NMR (Me₂SO-d₆) δ 2.90 (s, 3H, CH₃), 4.60 (s, 2H, CH₂), 5.73 (br s, 2H, NH₂), 7.11 (br m, 5H, NH₂, H⁶, H⁴, & H³), 7.41 (d, 2H, J = 8.3 Hz, aromatic), 7.65 (m, 2H, np), 7.77 (t, 1H, J = 7.8 Hz, np), 7.94 (d, 2H, J = 8.3 Hz, aromatic), 8.10 (d, 1H, J = 7.3 Hz, np), 8.32 (d, 1H, J = 8.1 Hz, np), 8.46 (dd, 1H, J = 0.9, 7.3 Hz, np), 8.53 (d, 1H, J = 8.1 Hz, np). Anal. (C₂₆H₂₃N₅O₂S) C, H, N, S. HRMS (C₂₆H₂₃N₅O₂S)⁺ calcd, 469.1575; found; 469.1569.

Example 13: Preparation of Compound 93

Compound 93 was prepared according to the following reaction scheme:

Preparation of Compound (88) --4-((2-Naphthyl)sulfonyl)toluene

4-((2-Naphthyl)sulfonyl)toluene (88) was prepared by the method of B. Graybill [*J. Org. Chem.* 32, 2931, (1967)]: 2-Naphthalene sulfonic acid, 70% (120 g, 0.40 mol), toluene (80 mL, 69 g, 0.75 mol, 1.3 eq.), and polyphosphoric acid (1 Kg)

were placed in a flanged reaction kettle with mechanical stirring and heated at 80°C for 16 h. The mixture was removed from the heat and poured into ice-water (2 L) and stirred until it attained ambient temperature. The resulting white precipitate was filtered off and recrystallized from EtOH (700 mL) to give 38.9 g (34%) of the product from the first crop and 10.9 g (10%) from the second. An analytical sample was prepared by recrystallization from EtOH, mp 160-162°C, [Lit: H. Meyer, *Justus Liebig's Annalen der Chemie*, 433 327 (1923) quotes 154°C]. NMR satisfactory. Anal. ($C_{17}H_{14}O_2S$) C, H, S.

Preparation of Compound (89) --

4-((2-Naphthyl)sulfonyl)benzyltoluene

4-((2-Naphthyl)sulfonyl)toluene (45.55 g, 0.161 mol) was dissolved in warm benzene (250 mL). H_2O (100 mL) was then added, and the mixture was brought to reflux. A few grains of AIBN were added to the mixture, and a 200 watt light was shone on it. Bromine (9.1 mL, 0.177 mol, 1.1 eq.) in benzene (90 mL) was then added dropwise during 30 min at a rate that maintained an orange-red color. The organic layer was separated, dried, and evaporated to give an off-white solid (50.4 g). TLC (SiO_2 - 40% EtOAc in hexane) showed some starting material present. The solid was used without further purification.

Preparation of Compound (90) --

N-Methyl-4-((2-naphthyl)sulfonyl)benzylamine
hydrobromide

Crude 4-((2-Naphthyl)sulfonyl)benzyl bromide (50.4 g, 0.14 mol) dissolved in THF (250 mL) was added dropwise to a stirred solution of 40% w/w aqueous methylamine (240 mL, 2.79 mol, > 20 eq) in THF (250 mL) during 40 min. The resulting mixture was evaporated to dryness to give a solid which was adsorbed onto gravity silica from DMF. This silica was loaded onto a 7 cm OD column packed with 3.5 in of SiO_2 . Unbrominated (88) was first eluted with EtOAc and then the product with MeOH. The appropriate fractions were evaporated to give the product as an amber solid (34.6 g, 54.8% from

88). An analytical sample was prepared by recrystallization of a small portion from EtOH/MeOH, m.p. 229-232°C, NMR (Me₂SO-d₆) δ 2.53 (s, 3H, CH₃), 4.19 (s, 2H, CH₂), 7.71 (m, 4H, aromatic), 7.90 (dd, 1H, J = 1.8, 8.6 Hz), 8.03 (d, 1H, J = 7.7 Hz), 8.12 (d, 3H, aromatic), 8.21 (d, 1H, J = 7.7 Hz), 8.73 (d, 1H, J = 1.0 Hz, np H¹), 8.84 (s, 1H, NH). Anal. (C₁₈H₁₈BrNO₂S) C, H, N, S, Br.

5-(N-(4-((2-Naphthyl)sulfonyl)benzyl)

Preparation of Compound (91) --
methylamino)-2-nitrobenzonitrile

A mixture of N-Methyl-4-((2-naphthyl)sulfonyl)benzylamine hydrobromide (16.8 g, 0.04 mol), 5-chloro-2-nitrobenzonitrile (7.7 g, 0.04 mol), and DMSO (16.8 mL) was warmed to 110°C with stirring until a solution was obtained. N,N-Diisopropylethylamine (11.1 mL, 0.06 mol, 1.5 eq.) was then added, and the solution kept at 110°C for 1 h. The mixture was cooled and poured into one third-saturated brine (300 mL). The yellow precipitate which formed was filtered off, washed with H₂O (200 mL) followed by Et₂O (200 mL), and dried in vacuo over P₂O₅ to give technical grade product (14.9 g, 77%). An analytical sample was prepared by flash chromatography of a small portion using 70% EtOAc in hexane followed by recrystallization from CH₃CN, mp 187-188°C, NMR (Me₂SO-d₆) δ 3.18 (s, 3H, CH₃), 4.89 (s, 2H, CH₂), 6.96 (dd, 1H, J = 2.9, 9.6 Hz, H⁴), 7.33 (d, 1H, J = 2.9 Hz, H⁶), 7.40 (d, 2H, J = 8.3 Hz, aromatic), 7.69 (dq, 2H, J = 1.5, 7.2 Hz, np), 7.88 (dd, 1H, J = 1.8, 8.7 Hz, np), 8.00 (m, 3H), 8.12 (m, 2H), 8.20 (d, 1H, J = 7.6 Hz), 8.69 (d, 1H, J = 1.1 Hz, np H¹). Anal. (C₂₅H₁₉N₃O₄S) C, H, N, S.

Preparation of Compound (92) --

2-Amino-5-(N-(4-((2-naphthyl)sulfonyl)benzyl)
methylamino)benzonitrile

Method A. KBH₄ (5.4 g, 100 mmol, 7 eq) was added during 30 min to a stirred solution of 5-(N-(4-((2-naphthyl)sulfonyl)benzyl)methylamino)-2-nitrobenzonitrile (6.5 g, 14 mmol) in a mixture of CH₂Cl₂ (300 mL), and MeOH (300 mL) containing CuCl (4.2 g, 40 mmol, 3 eq) in suspension. The

black mixture was stirred at 25°C for 1 h. It was then filtered, and the filtrate was poured into H₂O (400 mL) and extracted with CH₂Cl₂ (200 mL). The organic layer was washed with brine (500 mL), dried, and evaporated to give the technical grade product as a green-brown solid (5.57 g, 91%). Preparative TLC of a small portion using 80% EtOAc in hexane, followed by CH₃CN, as eluants, gave an analytical sample as an amorphous, dark yellow solid, mp >50°C dec, NMR (Me₂SO-d₆ δ 2.76 (s, 3H, CH₃), 4.43 (s, 2H, CH₂), 5.31 (s, 2H NH₂), 6.67 (m, 2H, H⁶ & H³), 6.89 (dd, 1H, J = 2.9, 9.1 Hz, H⁴), 7.40 (d, 2H, J = 8.2 Hz, aromatic), 7.69 (m, 2H, np), 7.87 (dd, 1H, J = 1.8, 8.6 Hz, np), 7.95 (d, 2H, J = 8.2 Hz, aromatic), 8.02 (d, 1H, J = 7.5 Hz, np), 8.11 (d, 1H, J = 8.6 Hz, np), 8.20 (d, 1H, J = 7.5 Hz, np), 8.69 (s, 1H, np H¹). Anal. (C₂₅H₂₁N₃O₂S) C, H, N, S.

Method B. To a solution of 4-((2-naphthyl)sulfonyl)benzyl bromide (89, 65%, 1.54 g, 2.77 mmol) in DMA (10 mL) at 45°C was added N,N-diisopropylethylamine (1.9 mL, 11.1 mmol, 4 eq) followed by 2-amino-5-(methylamino)benzonitrile (34, 0.45 g, 3.05 mmol, 1.1 eq). The resulting solution was stirred at 45-55°C for 1 h, during which time it changed color from yellow to green-brown. It was poured into H₂O (30 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with H₂O (10 mL) followed by brine (20 mL), dried, and evaporated to give a dark yellow foam (1.72 g). This was taken up in a minimal amount of CH₂Cl₂ and loaded onto a 3.5 cm OD column packed with 6 in SiO₂. The column was eluted with 40% EtOAc in hexane, and the appropriate fractions were combined and evaporated to give the product as a yellow foam (0.49 g, 41%). Its NMR spectrum was identical to that of the product from Method A and the products co-eluted on TLC (SiO₂/40% EtOAc in hexane, R_f=0.14).

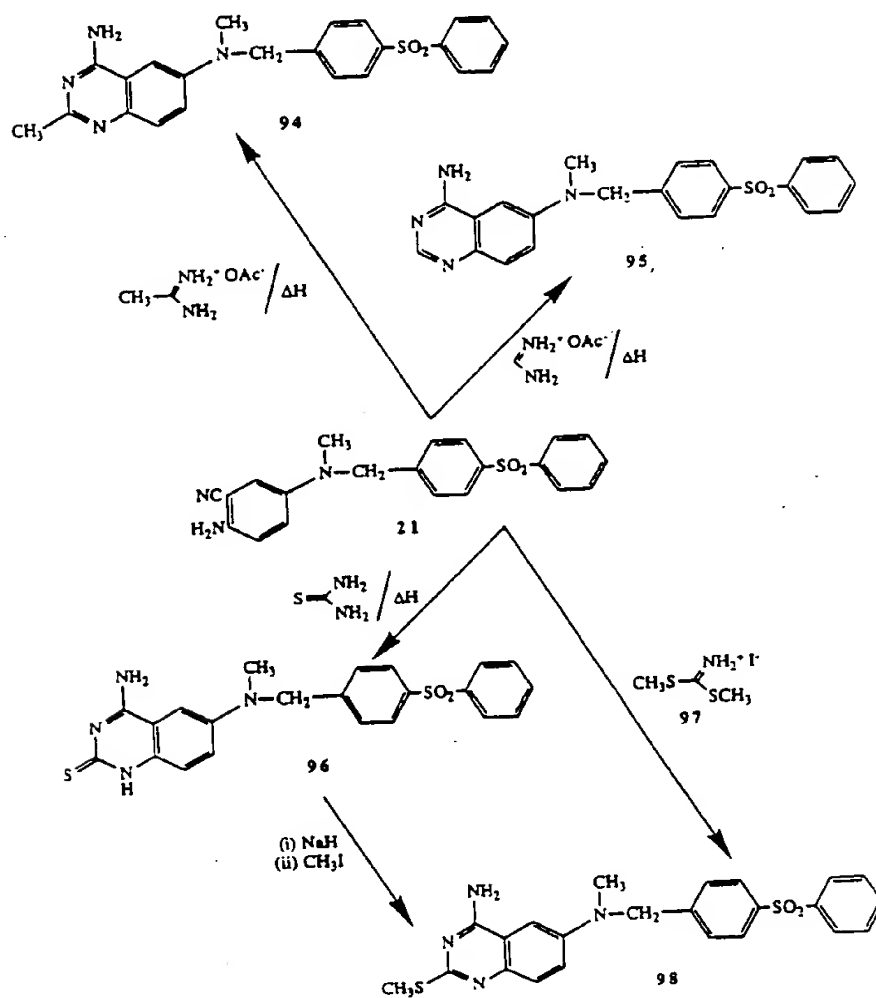
Preparation of Compound (93) --

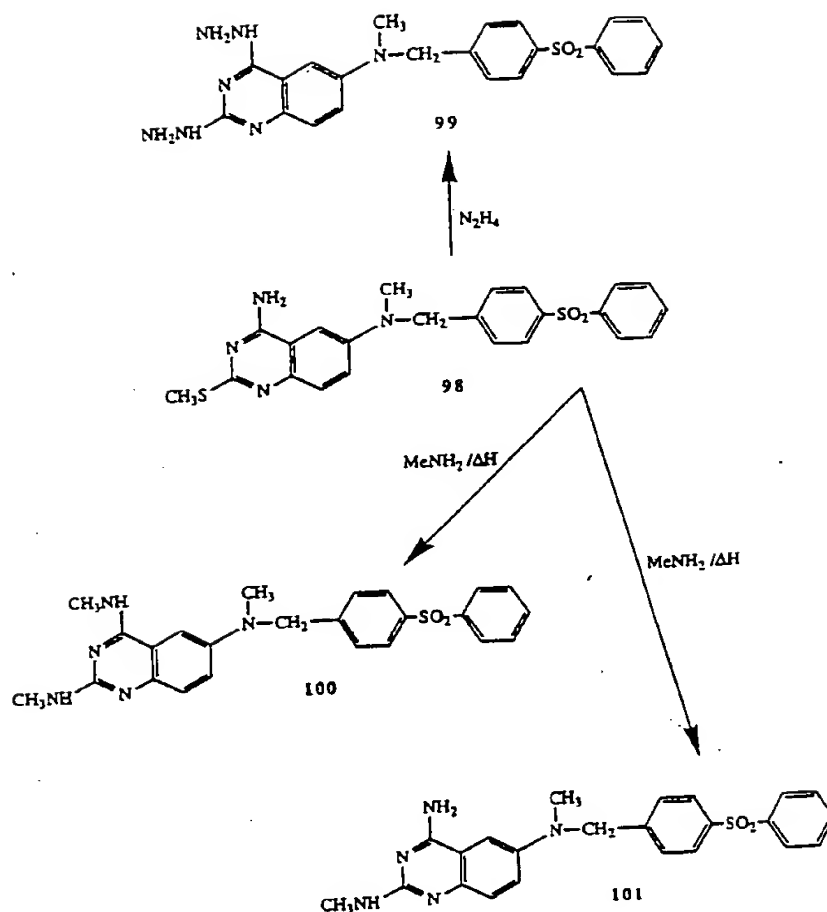
2,4-Diamino-6-((N-(4-(2-naphthyl)sulfonyl)
benzyl)methylamino)quinazoline

2-Amino-5-(N-(4-((2-naphthyl)sulfonyl)benzyl)methylamino)benzonitrile (10.0 g, 23 mmol) and diglyme (42 mL) were stirred at about 70°C for 20 min. Chlorformamidine hydrochloride (3.2 g, 28 mmol, 1.2 eq) was then added in portions during 15 min. The resulting mixture was heated at 150°C for 1.5 h with occasional manual stirring with a glass rod. The cooled mixture was triturated with Et₂O (150 mL). The ether was decanted, and the residue was dissolved in a warm mixture of DMF (100 mL) and Et₃N (10 mL). The resulting solution was treated with charcoal and filtered. The filtrate was poured onto a mixture of ice (500 g) and 10% NaOH (100 mL) and stirred until the ice melted. The resulting golden-yellow precipitate was filtered off and washed with H₂O. It was adsorbed onto gravity silica from DMF and loaded onto a 5 cm OD column packed with 5.5 in of SiO₂. The column was eluted with 4% Et₃N/8% MeOH/88% CH₂Cl₂. The best fractions were evaporated to give the product as a bright yellow solid (0.218 g, 2%), mp > 190°C dec. A second chromatography of material from impure fractions yielded further pure product (0.655 g, 6%). NMR (Me₂SO-d₆) δ 2.94 (s, 3H, CH₃), 4.65 (s, 2H, CH₂), 6.04 (br s, 2H, NH₂), 7.16 (br m, 5H, NH₂, H⁵, H⁷, & H⁸), 7.45 (d, 2H, J = 8.3 Hz, aromatic), 7.71 (m, 2H, np), 7.89 (dd, 1H, J = 1.7, 8.7 Hz, np), 7.98 (d, 2H, J = 8.3 Hz, aromatic), 8.04 (d, 1H, J = 7.7 Hz, np), 8.14 (d, 1H, J = 8.7 Hz, np), 8.22 (d, 1H, J = 7.7 Hz, np), 8.70 (s, 1H, np H¹). Anal. (C₂₆H₂₃N₅O₂S) C, H, N, S. HRMS (C₂₆H₂₃N₅O₂S)⁺ calcd, 469.1575; found, 469.1596.

Example 14: Preparation of Compounds 98-101

Compounds 98-101 were prepared according to the following reaction scheme:





**Preparation of Compound (94) --
4-Amino-2-methyl-6-(N-(4-(phenylsulfonyl)
benzyl)methylamino)quinazoline**

2-Amino-5-(N-(4-(phenylsulfonyl)benzyl)methylamino) benzonitrile (21, 4.32 g, 11.4 mmol) was dissolved in diglyme (20 mL) at 100°C . Acetamidine acetate (1.62 g, 13.7 mmol, 1.2 eq) was added, and the mixture was heated at 150°C for 4 h. It was cooled and partitioned between CH_2Cl_2 and H_2O . The organic layer was washed with brine, dried, and evaporated to give a solid which was adsorbed onto gravity silica from DMF. This silica was loaded onto a 7 cm OD column packed with 5 in SiO_2 . The column was eluted with 5% MeOH in CH_2Cl_2 . The appropriate fractions were charcoal treated and evaporated to give the product as a tan solid

(0.53 g, 11%), m.p. 262-263°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.34 (s, 3H, CH_3), 3.03 (s, 3H, N- CH_3), 4.74 (s, 2H, CH_2), 7.19 (d, 1H, $J = 2.5$ Hz, H^5), 7.29 (dd, 1H, $J = 2.5, 9.2$ Hz, H^7), 7.41 (m, 5H, NH_2 , H^8 , aromatic), 7.63 (m, 3H, aromatic), 7.92 (m, 4H, aromatic). Anal. ($\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$) C, H, N, S. HRMS ($\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$)⁺ calcd, 418.1463; found, 418.1479.

Preparation of Compound (95) --

4-Amino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

2-Amino-5-(N-(4-(phenylsulfonyl)benzyl)methylamino) benzonitrile (21, 4.32 g, 11.4 mmol) was dissolved in diglyme (20 mL) at 100°C with stirring. Formamidinium acetate (1.43 g, 13.7 mmol, 1.2 eq) was added, and the mixture was heated at 150°C for 4 h. It was cooled and partitioned between CH_2Cl_2 and H_2O . The organic layer was washed with brine, dried, and evaporated to give a solid which was adsorbed onto gravity silica from DMF. This silica was loaded onto a 7 cm OD column packed with 5 in SiO_2 . The column was eluted with 5% MeOH in CH_2Cl_2 . The appropriate fractions were charcoal treated and evaporated to give the product as a cream-colored solid (0.71 g, 15%), m.p. 217-218°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.05 (s, 3H, CH_3), 4.77 (s, 2H, CH_2), 7.20 (d, 1H, $J = 2.4$ Hz, H^5), 7.33 (dd, 1H, $J = 2.5, 9.2$ Hz, H^7), 7.45 (m, 5H, NH_2 , H^8 , aromatic), 7.63 (m, 3H, aromatic), 7.92 (m, 4H, aromatic), 8.15 (s, 1H, H^2). Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$) C, H, N, S. HRMS ($\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$)⁺ calcd, 404.1309; found, 404.1315.

Preparation of Compound (96) --

4-Amino-1,2-dihydro-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)-2-thioquinazoline

2-Amino-5-(N-(4-(phenylsulfonyl)benzyl)methylamino) benzonitrile (21, 1.0 g, 3 mmol) and thiourea (0.2 g, 3 mmol) were ground together in a mortar and pestle. The resulting powder was heated to fusion at 170°C for 5 h, and then allowed to cool to room temperature. The dark brown solid which formed was chiseled out and adsorbed onto gravity silica from DMF. This was twice flash chromatographed, first using 85% CH_3CN in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2 . The

appropriate fractions were evaporated to give the product as a yellow powder (0.089 g, 8%), mp 197-199°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.99 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.23 (s, 3H, aromatic), 7.41 (d, 2H, $J = 8.3$ Hz, aromatic), 7.62 (m, 3H, aromatic), 7.92 (m, 4H, aromatic), 8.17 (br s, 2H, NH_2), 12.30 (br s, 1H, NH). Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$) C, H, N, S. HRMS, FAB: thioglycerol/glycerol matrix, $(\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_2\text{S}_2)^+$ calcd, 437.1106; found, 437.1130.

Methyl dithiocarbamate was prepared by a published method [J. von Braun, *Berichte Deutschen Chemischen Gesellschaft*, 35 3368 (1902)]: MeI (8.5 mL, 0.136 mol, 1 eq) was added in one portion to a stirred suspension of ammonium dithiocarbamate (15.0 g, 0.136 mol) at room temperature. After 10 min, all solid had dissolved, and the resulting clear solution was concentrated to a volume of 75 mL at 60°C, poured into H_2O (600 mL), and extracted with Et_2O (2 x 150 mL). The dried extract was evaporated at 40°C to give a quantitative yield of the product as an oil which partially solidified upon standing (14.6 g). NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory. Anal. ($\text{C}_2\text{H}_5\text{NS}_2 \cdot 0.25 \text{H}_2\text{O}$) C, H, N, S.

Preparation of Compound (97) --

S,S-Dimethyldithiocarbiminium iodide

S,S-Dimethyldithiocarbiminium iodide (97) was prepared by a published method [M.M. Delepine, *Bull. Soc. Chim. Fr., Series 3*, 29 53 (1903)] using acetone as the solvent. To a solution of methyl dithiocarbamate (6.0 g, 56 mmol) in acetone (18 mL) at 10°C was added MeI (5.2 mL, 84 mmol, 1.5 eq) during 30 sec., and the resulting mixture was stirred at 25°C for 5 h. A white crystalline product formed, which was filtered off and washed with Et_2O (40 mL). Additional product which had precipitated from the filtrate was collected and washed with Et_2O (50 mL) to give a total yield of 9.15 g (66%), mp 128-130°C (Lit, op cit, 130-140°C dec), NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory. Anal. ($\text{C}_3\text{H}_8\text{INS}_2$) C, H, I, N, S.

Preparation of Compound (98)

4-Amino-2-methylthio-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

Method A A solution of 4-amino-1,2-dihydro-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)-2-thioquinazoline (69 mg, 0.16 mmol) in a mixture of THF (4.8 mL) and DMF (0.55 mL) was prepared under argon and cooled in ice. It was then cannulated into an ice-chilled flask containing NaH (3.8 mg, 0.16 mmol) under argon. The resulting mixture was stirred in ice for 1 h, and then treated with iodomethane (0.01 mL, 0.16 mmol) in THF (0.5 mL) by syringe. The mixture was removed from ice and stirred at ambient temperature for 1 h. The mixture was poured into brine (2 mL) and extracted with EtOAc (1 mL). The organic layer was washed with H₂O (2 mL) followed by brine (2 mL), dried treated with activated carbon, filtered, and evaporated to give a solid (40 mg). This was adsorbed onto gravity silica from DMF and loaded onto a 1 cm OD column packed with 5 in SiO₂. The column was eluted with 70% EtOAc in hexane. The appropriate fractions were evaporated to give the product as a bright yellow solid (23 mg, 32%), mp 180-182°C with softening from 154°C. This compound, upon storage for 5 months, was subsequently observed to melt at 216.5-217.5°C. NMR (Me₂SO-d₆) δ 2.43 (s, 3H, S-CH₃), 3.02 (s, 3H, CH₃), 4.74 (s, 2H, CH₂), 7.19 (d, 1H, J = 2.4 Hz, H⁵), 7.28 (dd, 1H, J = 2.4, 9.1 Hz, H⁷), 7.37 (d, 1H, J = 9.1 Hz, H⁸), 7.43 (d, 2H, J = 8.3 Hz, aromatic), 7.64 (m, 5H, NH₂, aromatic), 7.93 (m, 4H, aromatic). Anal. (C₂₃H₂₂N₄O₂S₂) C, H, N, S. HRMS (C₂₃H₂₂N₄O₂S₂)⁺ calcd, 450.1171; found, 450.1187.

Method B A solution of 2-amino-5-(N-(4-(phenylsulfonyl)benzyl)methylamino)benzonitrile (21, 3.19 g, 8.45 mmol) and S,S,-dimethyldithiocarbiminium iodide (97, 4.21 g, 16.90 mmol, 2 eq) in DMF (16 mL) was stirred at room temperature under argon for 114 h, poured into H₂O (250 mL), and extracted with EtOAc (4 x 100 mL). An orange-colored oily residue which adhered to the empty separatory funnel was dissolved in MeOH (25 mL) to give a solution from which a

yellow solid precipitated within 5 min. Et₂O (100 mL) was added to this methanolic mixture, and the solid was filtered off and washed with Et₂O (100 mL) to give product (1.08 g). The combined EtOAc layers were decanted from a precipitated solid which had formed. This solid was dissolved in MeOH (50 mL), and the resulting solution was combined with the EtOAc extract, dried, and concentrated to a volume of 20 mL. Et₂O (200 mL) was added to precipitate a solid product which was filtered off, washed with Et₂O (100 mL), and dried (1.52 g). Both batches of product were lemon-yellow solids and of single-spot purity by TLC (SiO₂/30% hexane in EtOAc). Total yield 2.60 g (68%). The analytical sample was prepared by chromatography on SiO₂ using 30% hexane in EtOAc as eluant, mp 176-180°C with softening from 159°C; a mixed mp with the higher-melting form from Method A melted at 199°C with softening from 189°C. NMR (Me₂SO-d₆) identical to that of Method A. Anal. (C₂₃H₂₂N₄O₂S₂) C, H, N, S.

Preparation of Compound (99)

2,4-Bis(hydrazino)-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

A solution of 98 (500 mg, 1.1 mmol) and hydrazine (0.35 mL, 11 mmol, 10 eq) in a mixture of MeOH (8 mL) and THF (8 mL) in a pressure tube was stirred at 100°C. Additional hydrazine (0.35 mL, 11 mmol, 10 eq) was added after 3 h. At 23 h, a pale yellow solid had appeared, and the reaction was stopped. The solid was filtered off, washed with THF (2 x 25 mL) followed by Et₂O (2 x 25 mL), and dried to give the product (135 mg, 27.3%), mp 288°C dec, NMR (Me₂SO-d₆) δ 3.02 (s, 3H, CH₃), 4.71 (s, 2H, CH₂), 7.22 (d, 1H, J = 9.0 Hz, H⁷), 7.26 (s, 1H, H⁵), 7.40 (d, 2H, J = 8.2 Hz, aromatic), 7.59-7.69 (m, 4H, H⁸, aromatic), 7.90-7.95 (m, 4H, aromatic), 9.56 (s, 1H, NH), remaining NH protons not discernible. Anal. (C₂₂H₂₃N₇O₂S · 2H₂O) C, N, S; H: calcd, 5.60; found 4.80. 4.84. HRMS, DCI: (C₂₂H₂₄N₇O₂S)⁺ calcd, 450.1712; found 450.1716.

Preparation of Compound (100) --

2,4-Bis(methylamino)-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

A solution of 98 (500 mg, 1.1 mmol) and MeNH₂ (1 mL, 22.5 mmol, 20 eq) in a mixture of MeOH (5 mL) and THF (2 mL) was heated in a pressure tube at 110°C for 70 h and then at 150°C for 24 h. When cool, the dark brown solution was evaporated to give a crude oily residue (1.08 g) which was chromatographed on alumina (100 g) using 4% MeOH in CH₂Cl₂ to give the technical grade product, which was further purified by chromatography on SiO₂ (20 g) using EtOAc to elute impurities followed by MeOH to elute the pure product as a yellow-orange solid (126 mg, 26%), mp 124-126°C. NMR (Me₂SO-d₆) δ 2.78 (d, 3H, J = 4.6 Hz, HNCH₃), 2.92 (m, 6H, HNCH₃, NCH₃), 4.64 (s, 2H, CH₂), 6.22 (s, 1H, NH), 7.14 (m, 3H, H⁵, H⁷, & H⁸), 7.43 (d, 2H, J = 8.3 Hz, aromatic), 7.58-7.70 (m, 4H, NH & aromatic), 7.89-7.95 (m, 4H, aromatic). Anal. (C₂₄H₂₅N₅O₂S · 0.8H₂O) C, H, N, S. HRMS, FAB: thioglycerol/glycerol matrix, (C₂₄H₂₆N₅O₂S)⁺ calcd, 448.1807; found, 448.1803.

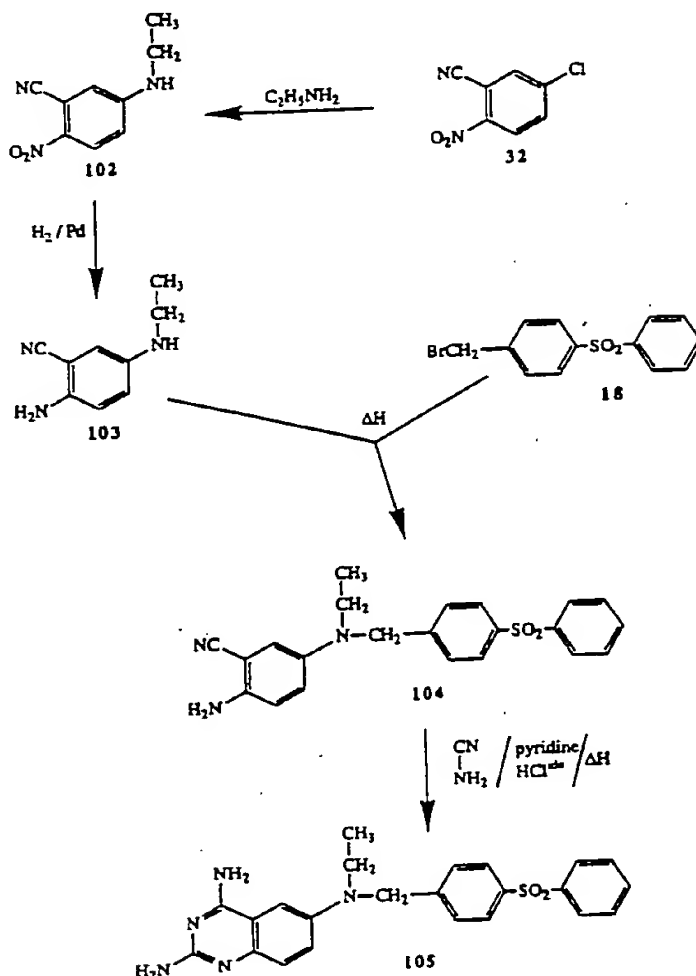
Preparation of Compound (101) --

4-Amino-2-(methylamino)-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline

A solution of 98 (250 mg, 0.55 mmol) and MeNH₂ (0.5 mL, 11.2 mmol, 20.4 eq) in a mixture of MeOH (2.5 mL) and THF (1 mL) was heated in a pressure tube at 130°C for 19 h. Removal of solvent gave a crude orange-colored solid (262 mg) which was chromatographed on alumina with 4% MeOH in CH₂Cl₂ as eluant to give the desired product as an orange-colored solid (40 mg, 16.8%), mp 130-132°C, NMR (Me₂SO-d₆) δ 2.76 (d, 3H, J = 4.7 Hz, HNCH₃), 2.92 (s, 3H, CH₃), 4.63 (s, 2H, CH₂), 6.01 (s, 1H, NH), 7.08 (s, 2H, NH₂), 7.14 (s, 3H, H⁵, H⁷, & H⁸), 7.44 (d, 2H, J = 8.4 Hz, aromatic), 7.58-7.89 (m, 3H, aromatic), 7.92-7.95 (m, 4H, aromatic). Anal. (C₂₃H₂₃N₅O₂S · 0.7 H₂O) C, H, N, S. HRMS, DCI: (C₂₃H₂₄N₅O₂S)⁺ calcd. 434.1651; found, 434.1640.

Example 15: Preparation of Compound 105

Compound 105 was prepared according to the following reaction scheme:

Preparation of Compound (102) --5-(Ethylamino)-2-nitrobenzonitrile

A solution of 5-chloro-2-nitrobenzonitrile (10.04 g, 0.055 mol) and EtNH_2 (45 mL, 0.69 mol, 12.5 eq) in DMSO (60

mL) was heated at 80°C for 1 h and then poured into H₂O (800 mL). Solid NaCl was added, and the mixture was extracted with EtOAc (2 x 500 mL), dried, and evaporated to give an orange-colored solid which was shaken with Et₂O (50 mL), filtered off, and washed with Et₂O (200 mL) to give the pure product as a bright, lemon-yellow solid (8.27 g, 78.7%), mp 169-171°C, NMR (Me₂SO-d₆) δ 1.18 (t, 3H, J = 7.2 Hz, CH₃), 3.18-3.27 (m, 2H, CH₂), 6.86 (dd, 1H, J = 9.4, 2.6 Hz, H⁴), 7.08 (d, 1H, J = 2.6 Hz, H⁶), 7.71 (t, 2H, J = 5.1 Hz, NH), 8.14 (d, 1H, J = 9.4 Hz, H³). Anal. (C₉H₉N₃O₂) C, H, N.

Preparation of Compound (103) --

2-Amino-5-(ethylamino)benzonitrile

A partial suspension of 5-(ethylamino)-2-nitrobenzonitrile (8.27 g, 43.2 mmol) in a mixture of EtOH (180 mL) and THF (50 mL) containing 10% Pd:C (0.82 g) was stirred under H₂ for 3 h. Filtration and evaporation gave the product as a light brown oil (6.33 g, 91%). An analytical sample was prepared by chromatography of a small portion of SiO₂ with 50% EtOAc in hexane to give the product as a light yellow oil. NMR (Me₂SO-d₆) δ 1.09 (t, 3H, J = 7.1 Hz, CH₃), 2.90 (q, 2H, CH₂), 5.02 (s, 1H, NH), 5.12 (s, 2H, NH₂), 6.46 (d, 1H, J = 2.6 Hz, H⁶), 6.64 (d, 1H, J = 8.9 Hz, H³), 6.72 (dd, 1H, J = 8.9, 2.6 Hz, H⁴). Anal. (C₉H₁₁N₃) C, H, N.

Preparation of Compound (104) --

2-Amino-5-(N-(4-(phenylsulfonyl)benzyl)
ethylamino)benzonitrile

A solution of 2-amino-5-(ethylamino)benzonitrile (1.61 g, 10 mmol), 4-(phenylsulfonyl)benzyl bromide (18, 66%, 5.18 g, 11 mmol, 1.1 eq), and N,N-diisopropylethylamine (1.92 mL, 11 mmol, 1.1 eq) in DMA (10 mL) was stirred under argon at 80°C for 55 min. The mixture was poured into weak brine (175 mL) and extracted with EtOAc (2 x 50 mL). The extracts were charcoal treated and evaporated to give a crude dark brown oil (5.9 g) which was chromatographed on SiO₂ (300 g) using 50% EtOAc in hexane as the eluant. The appropriate fractions were combined and evaporated to give the technical grade

product as a viscous, orange-colored oil. A pure fraction was evaporated separately to give the analytical sample as a gummy solid, mp 44-46°C. Total yield 1.86 g (48%), NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.00 (t, 3H, $J = 7.0$ Hz, CH_3), 3.26 (q, 2H, $J = 7.0$ Hz, CH_2), 4.41 (s, 2H, CH_2), 5.30 (s, 2H, NH_2) 6.64 (d, 1H, $J = 2.9$ Hz, H^6), 6.68 (d, 1H, $J = 9.1$ Hz, H^3), 6.85 (dd, 1H, $J = 9.1, 2.9$ Hz, H^4), 7.44 (d, 2H, $J = 8.4$ Hz, aromatic), 7.58-7.68 (m, 3H, aromatic), 7.88-7.95 (m, 4H, aromatic).
Anal. ($\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$) C, H, N, S.

Preparation of Compound (105) --

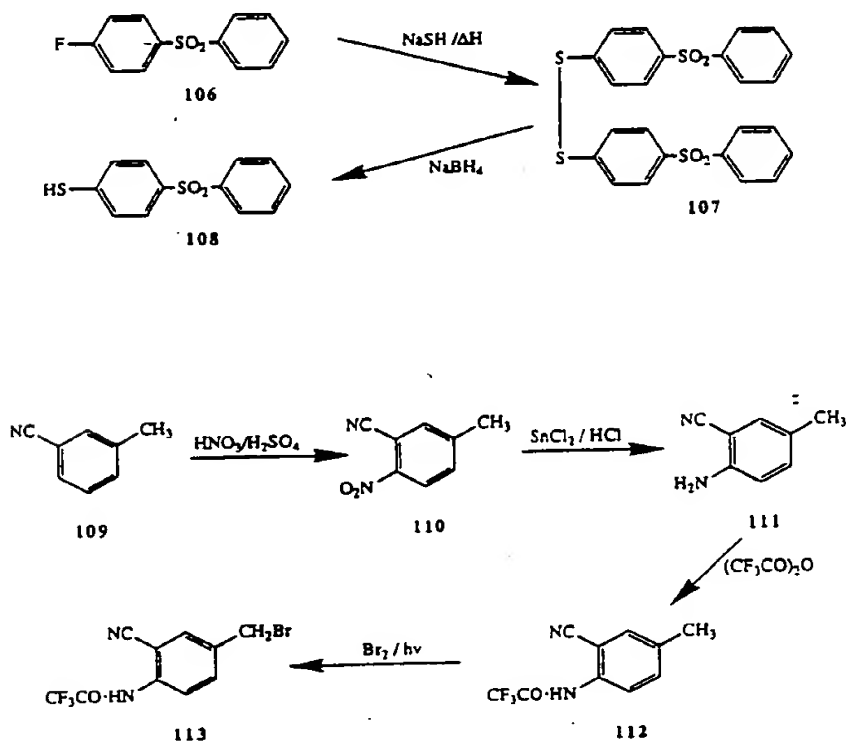
2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)
ethylamino)quinazoline

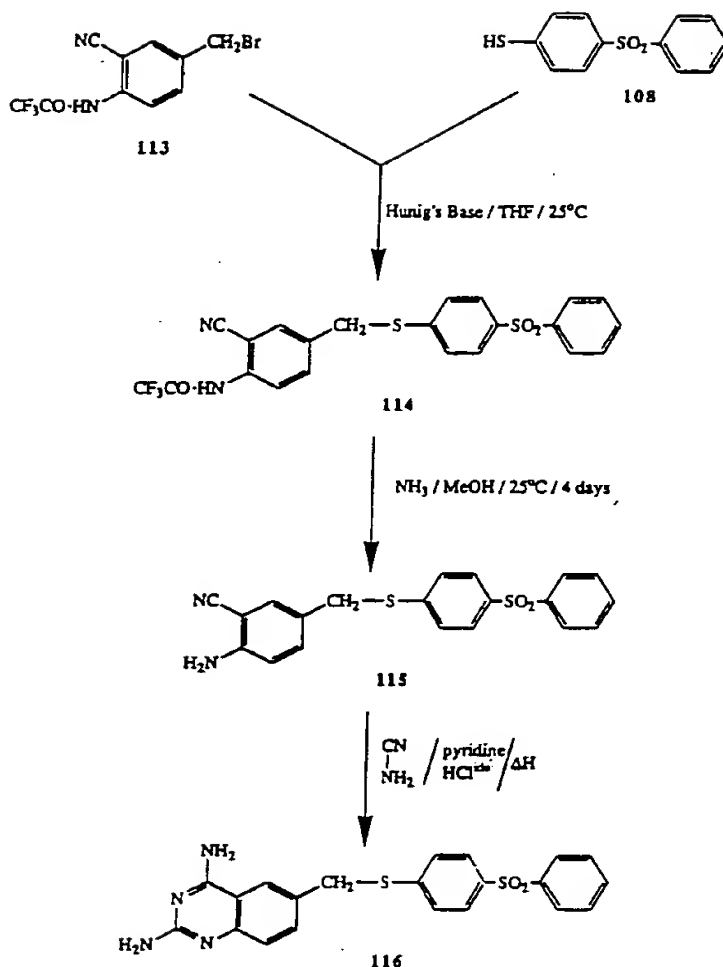
A mixture of 2-amino-5-(N-(4-(phenylsulfonyl)benzyl)ethylamino)benzonitrile (1.62 g, 4.1 mmol), pyridine hydrochloride (2.87 g, 24.8 mmol, 6 eq) and cyanamide (0.70 g, 16.6 mmol, 4.1 eq) was heated at 160°C to give a brown melt which thickened to a gelatinous mass after 10 min. At 17 min, the mass was removed from the heat and treated with boiling EtOH (10 mL) for 1 min; Et_3N (4.6 mL, 33 mmol, 8 eq) was then added. The mixture was cooled in ice, and more EtOH (20 mL) was added. The orange-colored solid which had formed upon cooling was filtered off, washed with cold EtOH (30 mL) followed by Et_2O (50 mL), and dried (166 mg). To the filtrate was added Et_2O (50 mL) to give a second crop which was filtered off, washed with Et_2O (50 mL), and dried (610 mg). The second filtrate was further treated with Et_2O (100 mL) to give a yellow-orange, sticky solid from which the mother liquor was decanted. This solid was triturated with acetone (100 mL), filtered off, and washed with acetone (2 x 200 mL) followed by Et_2O (2 x 20 mL), and dried to give a third crop of material (1.7 g). The three crops were combined and dissolved in MeOH (100 mL) and coated onto alumina (15 g) and chromatographed on alumina (200 g) using 10-30% MeOH in CH_2Cl_2 as eluant to give a yellow-orange solid. This was further purified by boiling a slurry of it in MeOH (10 mL) for 10 sec., and then cooling it in ice. The resulting solid was filtered off and washed sequentially with

MeOH (10 mL) and Et₂O (10 mL) to give the product as a yellow solid (398 mg, 22 %), mp 216-218°C. NMR (Me₂SO-*d*₆) δ 1.07 (t, 3H, J = 6.9 Hz, CH₃), 3.40 (q, 2H, J = 6.9 Hz, CH₂), 4.58 (s, 2H, CH₂), 5.59 (s, 2H, NH₂), 7.04-7.07 (m, 4H, H⁷, H⁸, & NH₂), 7.14 (s, 1H, H⁵), 7.47 (d, 2H, J = 8.3 Hz, aromatic), 7.57-7.70 (m, 3H, aromatic), 7.89-7.95 (m, 4H, aromatic).
 Anal. (C₂₃H₂₃N₅O₂S · 0.8 H₂O) C, H, N, S. HRMS, FAB: nitrobenzyl alcohol matrix, (C₂₃H₂₄N₅O₂S)⁺ calcd, 434.1651; found, 434.1638.

Example 16: Preparation of Compound 116

Compound 116 was prepared according to the following reaction scheme:





Preparation of Compound (107) --

Bis-(4-(phenylsulfonyl)phenyl) disulfide

A solution of 4-fluorophenyl phenyl sulfone (106, 20.0 g, 0.08 mol) and anhydrous sodium hydrosulfide (Strem Chemicals, Inc., 5.2 g, 0.09 mol, 1.1 eq) in DMSO (150 mL) was stirred at 90°C for 1 h, and was then poured into H₂O (600 mL). A viscous gob precipitated which was mechanically

removed and dissolved in EtOAc (400 mL). The aqueous solution remaining was extracted with CH_2Cl_2 (2 x 250 mL). All the organic layers were combined, concentrated to about 500 mL, washed with H_2O (2 x 200 mL) followed by brine (200 mL), dried, treated with carbon, filtered through celite, and evaporated. Part way through evaporation, some EtOH (about 10 mL) was added to the solution to induce formation of a better quality solid. A yellow solid was obtained which was recrystallized from EtOAc/EtOH to give the product as a white solid (10.34 g, 49%), mp 137-138°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 7.61-7.74 (m, 10H, aromatic), 7.94 (m, 8H, aromatic). Anal. ($\text{C}_{24}\text{H}_{18}\text{S}_4\text{O}_4$) C, H, S.

Preparation of Compound (108) --

4-(Phenylsulfonyl)thiophenol

NaBH_4 (0.92 g, 24 mmol, 2.5 eq) was added to a warm solution of the disulfide 107 (4.8 g, 9.7 mmol) in THF (40 mL), and the resulting mixture was brought to reflux. MeOH (8 mL) was then added dropwise during 30 min; a gas evolved. The mixture was heated under reflux for 3 h and then cooled. It was treated with 1N HCl (40 mL), then 6N HCl (60 mL), and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with H_2O (150 mL) then brine (150 mL), dried, evaporated, and vacuum pumped dry to give a crude product (4.5 g, 91%), which was used without further purification. An analytical sample was recrystallized from EtOH to give off-white crystals, mp 120.5-122.5°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 6.24 (br s, 1H, SH), 7.53 (d, 2H, $J = 8.3$ Hz, H^2 & H^6), 7.59-7.69 (m, 3H), 7.81 (d, 2H, $J = 8.3$ Hz, H^3 & H^5), 7.94 (dd, 2H, $J = 1.6, 7.0$ Hz). Anal. ($\text{C}_{12}\text{H}_{10}\text{O}_2\text{S}_2$) C, H, S.

Preparation of Compound (110) --

5-Methyl-2-nitrobenzonitrile

Nitric acid (70%, 250mL) was added dropwise during 30 min to a mechanically stirred solution of m-tolunitrile (102 mL, 0.853 mol) in conc H_2SO_4 (330mL) keeping the temperature of the reaction mixture between -20°C and 0°C. The resulting viscous mixture was stirred for 1 hr at -5°C and then poured

into ice/water (2 L). The resulting off-white precipitate was filtered off and washed with H_2O (3 x 2 L); it was then allowed to steep in H_2O (2 L) overnight. It was filtered off from a pH-neutral filtrate and pressed dry and dried over P_2O_5 in vacuo. This crude product (147.02 g) was recrystallized twice from EtOH to give the pure product as off-white needles (56.74g, 41%), mp 91-92°C, [Lit: W. Findekle, *Berichte Deutschen Chemischen Gesellschaft*, 38 3544 (1905) quotes 93-94°C; P. Pfeiffer, *ibid*, 51 559 (1918) quotes 92-93°C]. NMR ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 7.59 (d, 1H, J = 7.3 Hz, H^4), 7.71 (d, 1H, J = 1.1 Hz, H^6), 8.24 (d, 1H, J = 8.5 Hz, H^3).

Preparation of Compound (111) --

2-Amino-5-methylbenzonitrile

To $SnCl_2 \cdot 2H_2O$ (225.65 g, 1 mol, 4 eq) dissolved in conc. HCl (300 mL) was added 5-methyl-2-nitrobenzonitrile (110, 40.54 g, 0.25 mol) in portions during 1.5 h with ice cooling to keep the temperature at about 25°C. The mixture was stirred for 2 h at 25°C and then poured into ice/water (1L). 1N NaOH (1 L) was added with stirring followed by solid NaOH to give pH14. At this pH, a cream-colored precipitate formed which was extracted with EtOAc (3 x 2 L). The combined extracts were concentrated to about 1 L, washed with H_2O (2 x 500 mL) followed by brine (500 mL), dried, filtered, and evaporated to give a thick, clear, yellow liquid. This was put under vacuum for 2 days to give the crude crystalline product (30.8 g). This was recrystallized from EtOH to give off-white microneedles (10.23 g, 31%, plus a second crop of 5.0 g, 15%), mp 61-63°C. [Lit: W. Findekle, *Berichte Deutschen Chemischen Gesellschaft*, 38 3544 (1905) quotes 63°C]. NMR (Me_2SO-d_6) δ 2.09 (s, 3H, CH_3), 5.76 (br s, 2H, NH_2), 6.66 (d, 1H, J = 8.5 Hz, H^3), 7.08 (dd, 1H, J = 2.0 Hz, 8.5 Hz, H^4), 7.13 (s, 1H, H^6)

Preparation of Compound (112) --

5-Methyl-2-((trifluoroacetyl)amino)benzonitrile

Trifluoroacetic anhydride (0.59 mL, 4.16 mmol, 1.1eq) was added dropwise during 15 min to a stirred solution of 2-amino-5-methylbenzonitrile (111, 500 mg, 3.78 mmol) and Et₃N (0.58 mL, 4.2 mmol, 1.1eq) in CH₂Cl₂ (5 mL) in an ice bath. The resulting mixture was then stirred at 25°C for 30 min. It was treated with 1N HCl (5 mL) to give pH <2. The organic layer was separated, washed with satd NaHCO₃ (5 mL), dried, filtered, and evaporated to give the product as white, feathery needles which were dried in vacuo (0.86 g, 100%) mp 122-124°C, NMR (Me₂SO-d₆) δ 2.39 (s, 3H, CH₃), 7.47 (d, 1H, J = 8.2 Hz, H³), 7.64 (d, 1H, J = 8.2 Hz, H⁴), 7.80 (s, 1H, H⁶), 11.69 (s, 1H, NH). Anal. (C₁₀H₇F₃N₂O) C, H, N.

Preparation of Compound (113) --

5-(Bromomethyl)-2-((trifluoroacetyl)amino)benzonitrile

The toluene 112 (13.11 g, 57.5 mmol) was dissolved in warm benzene (50 mL). H₂O (25 mL) was added, and the mixture was brought to reflux. A 200 watt light was shone on it, and a solution of bromine (3.26 mL, 63.2 mmol, 1.1eq) in benzene (25 mL) was added dropwise during 45 min at a rate that maintained an orange-red color. The organic layer was separated, dried, and evaporated to give a pale yellow, feathery, crystalline solid which was dried in vacuo over P₂O₅ (13.92 g). It was used without further purification.

Preparation of Compound (114) --

5-((4-(Phenylsulfonyl)phenylthio)methyl)-2-((trifluoroacetyl)amino)benzonitrile

Diisopropylethylamine (5.45 mL, 31.3 mmol, 1.1eq) was added to the crude thiol 108 (7.12 g, <28.4 mmol) dissolved in THF (30 mL), and the resulting mixture was stirred for 10 min. The crude bromide 113 (8.28 g, <28.4 mmol) was then added in portions during 5 min, and the resulting mixture was stirred at 25°C for 1 h. It was then poured into H₂O (80 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with brine, dried, and evaporated to give

an off-white foam which was dried in vacuo over P_2O_5 to give the crude product (13.06 g). This was adsorbed onto gravity silica from CH_3CN and loaded onto a 7 cm OD column packed with 6 in of SiO_2 ; the column was eluted with 10% CH_3CN in toluene. The best fractions were evaporated to give the pure product as a white microcrystalline solid (3.58 g, 23% from the disulfide 107), mp 154.5-156.5°C. A second chromatography of material from impure fractions yielded further pure product (1.02 g, 6.5%), NMR (Me_2SO-d_6) δ 4.45 (s, 2H, CH_2), 7.53-7.68 (m, 6H, aromatic), 7.83-7.99 (m, 6H, aromatic), 11.73 (s, 1H, NH), Anal. ($C_{22}H_{15}F_3N_2O_3S_2$) C, H, N, S.

Preparation of Compound (115) --

2-Amino-5-((4-phenylsulfonyl)phenylthio)
methylbenzonitrile

NH_3 gas was bubbled for about 1 min through a solution of the amide 114 (2.68 g, 5.62 mmol) in MeOH (30 mL). The solution, which became warm to the touch, was stirred at 25°C for 4 days. It was then treated with 1N NaOH (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with H_2O (2 x 100 mL) followed by brine (100 mL), dried, filtered, and evaporated to give the product as a white crystalline solid which was dried in vacuo (1.66 g, 78%), mp 170-171°C, NMR (Me_2SO-d_6) δ 4.20 (s, 2H, CH_2), 6.10 (s, 2H, NH_2), 6.73 (d, 1H, $J = 8.6$ Hz, H^3), 7.33 (dd, 1H, $J = 2.0$ Hz, 8.6 Hz, H^4), 7.41 (d, 1H, $J = 2.0$ Hz, H^6), 7.48 (d, 2H, $J = 8.5$ Hz, aromatic), 7.64 (m, 3H, aromatic), 7.83 (d, 2H, $J = 8.5$ Hz, aromatic), 7.93 (d, 2H, $J = 8.5$ Hz, aromatic). Anal. ($C_{20}H_{16}N_2O_2S_2$) C, H, N, S.

Preparation of Compound (116) --

2,4-Diamino-6-((4-phenylsulfonyl)phenylthio)
methylquinazoline

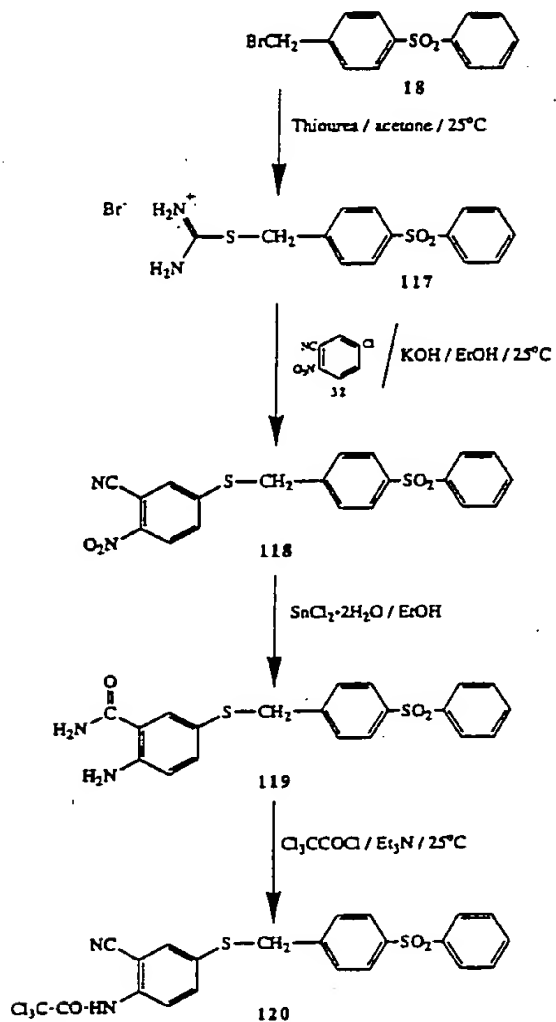
A mixture of the aminonitrile 115 (100 mg, 0.26 mmol), pyridine hydrochloride (182 mg, 1.58 mmol, 6 eq), and cyanamide (44 mg, 1.05 mmol, 4 eq) was homogenized with a glass rod in a 25 mL round bottom flask, which was then immersed in a 165°C oil bath for 5 min. A melt resulted which was cooled to room temperature, whereupon it became a

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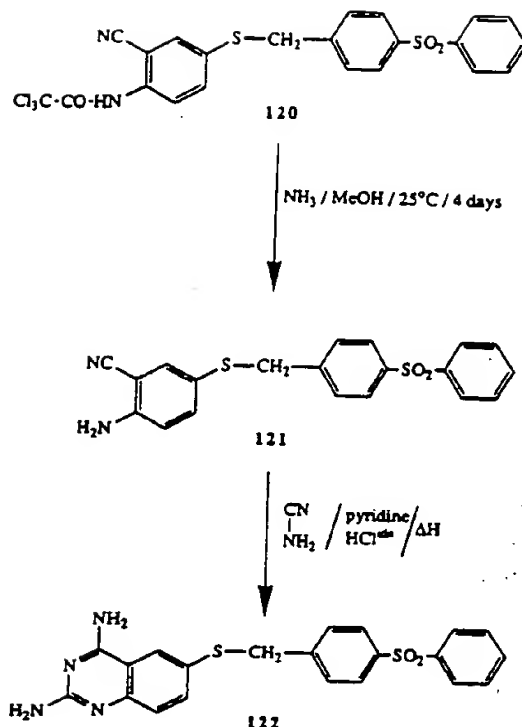
sludge. EtOH (5 mL) was added, and the mixture was heated to boiling while being worked with a glass rod. Et₃N (0.29 mL, 2.10 mmol, 8 eq) was then added, and the mixture boiled further; a yellow precipitate formed. The mixture was cooled and put on ice. The precipitate was filtered off, washed with EtOH (10 mL) followed by Et₂O (10 mL), and dried in vacuo over P₂O₅ to give a crude product (36 mg). Meanwhile, light yellow microneedless had formed in the filtrate. These were filtered off, washed with EtOH followed by Et₂O, and dried. TLC showed this to be the same substance as the original precipitate, and NMR showed it to be more pure (43 mg, 38%), mp 251.5-254°C with darkening from 215°C, NMR (Me₂SO-d₆) δ 4.33 (s, 2H, CH₂), 6.04 (br s, 2H, NH₂), 7.14 (d, 1H, J = 8.6 Hz, H⁸), 7.29 (br s, 2H, NH₂), 7.50-7.68 (m, 6H, aromatic), 7.83 (d, 2H, J = 8.4 Hz, aromatic), 7.92 (d, 2H, J = 7.3 Hz, aromatic), 8.00 (s, 1H, H⁵). Anal. (C₂₁H₁₈N₄O₂S₂) C, H, N, S. HRMS, FAB: nitrobenzyl alcohol matrix, (C₂₁H₁₉N₄O₂S₂)⁺ calcd, 423.0949; found, 423.0960.

Example 17: Preparation of Compound 122

Compound 122 was prepared according to the following reaction scheme:



-105-



Preparation of Compound (117) --

S-(4-Phenylsulfonyl)benzylisothiuronium bromide

4-(Phenylsulfonyl)benzyl bromide (18, 100 mg, 0.33 mmol) was added to a solution of thiourea (25 mg, 0.33 mmol) in acetone (1 mL) at 25°C. The mixture was stirred for 3 h, whereupon a precipitate gradually formed. The mixture was diluted with Et₂O (10 mL), and the resulting precipitate was filtered off, washed with Et₂O, and dried to give the product as a white, microcrystalline solid (77 mg, 60%), mp 204-206°C, NMR (Me₂SO-d₆) δ 4.55 (s, 2H, CH₂), 7.68 (m, 5H, aromatic), 7.97 (m, 4H, aromatic), 9.00 (s, 2H, NH₂), 9.21 (s, 2H, NH₂). Anal. (C₁₄H₁₅BrN₂O₂S₂) C, H, N, S, Br.

Preparation of Compound (118) --

2-Nitro-5-((4-(phenylsulfonyl)benzyl)thio)benzonitrile

To a suspension of the salt 117 (3.44 g, 8.88 mmol) and 5-chloro-2-nitrobenzonitrile (1.62 g, 8.88 mmol) in EtOH (30 mL) was added a solution of KOH (85%, 1.17g, 17.6 mmol, 2 eq) dissolved in EtOH (8 mL). The reaction mixture turned dark

yellow, then green-brown, and finally dark red, with precipitation of a solid, which, however, contained mainly starting aryl chloride by TLC. The mixture was stirred at 25°C for 3 days. The solid, now largely product, was filtered off and washed with H₂O (500 mL) and dried in vacuo over P₂O₅. It was adsorbed onto gravity silica from DMF and loaded onto a 4 cm OD column packed with 6 in SiO₂. The column was eluted with 40% EtOAc in hexane, and the best fractions were evaporated to give a yellow solid (0.470 g, 13%) which was recrystallized from EtOH to give the analytical sample, m.p. 181.5-183.5°C. Less good fractions provided a slightly impure product (1.09 g, 30%) which was used without further purification. NMR (Me₂SO-d₆) δ 4.62 (s, 2H, CH₂), 7.66 (m, 5H, aromatic), 7.80, (dd, 1H, J = 2.2, 8.8 Hz, H⁴), 7.94 (d, 4H, J = 8.1 Hz, aromatic), 8.12 (d, 1H, J = 2.2 Hz, H⁶), 8.24 (d, 1H, J = 8.8 Hz, H³). Anal. (C₂₀H₁₄N₂O₄S₂) C, H, N, S.

Preparation of Compound (119) --

2-Amino-5-((4-(phenylsulfonyl)benzyl)thio)benzamide

A mixture of the nitrobody 118 (1.31 g, 3.19 mmol), SnCl₂·2H₂O (3.60 g, 16.0 mmol, 5 eq), and EtOH (6.5 mL) was stirred at 70°C for 3 h and then cooled. The mixture was poured into iced H₂O (25 mL), whereupon a yellow precipitate formed. 1N NaOH (22 mL) was added to give pH 14, and the precipitate was then filtered off and washed with H₂O (40 mL). The precipitate was resuspended in 1N NaOH (20 mL), filtered off, washed sequentially with H₂O (40 mL), EtOH (10 mL), and Et₂O (10mL), and dried in vacuo over P₂O₅. The crude product (1.06 g, 83%) so obtained was used without further purification. An analytical sample was prepared by recrystallization from EtOH to give off-white microneedles, mp 202-205°C, NMR (Me₂SO-d₆) δ 4.07 (s, 2H, CH₂), 6.55 (d, 1H, J = 8.5 Hz, H³), 6.75 (br s, 2H, NH₂), 6.99 (dd, 1H, J = 2.1, 8.5 Hz, H⁴), 7.11 (br s, 1H, NH), 7.40 (d, 2H, J = 8.4 Hz, aromatic), 7.59-7.68 (m, 4H, H⁶ & aromatic), 7.79 (br s, 1H, NH), 7.83 (dd, 2H, aromatic), 7.91 (dd, 2H, J = 1.3, 8.3 Hz, aromatic). Anal. (C₂₀H₁₈N₂O₃S₂) C, H, N, S.

Preparation of Compound (120) --
5-((4-(Phenylsulfonyl)benzyl)thio)-2-
((trichloroacetyl)amino)benzonitrile

A solution of trichloroacetyl chloride (0.29 mL, 2.64 mmol, 1.1 eq) in CH_2Cl_2 (3 mL) was added dropwise during 1 h to a solution of the anilide 119 (0.95 g, 2.4 mmol) and Et_3N (0.67 mL, 4.8 mmol, 2 eq) in CH_2Cl_2 (4 mL). The resulting solution was stirred for 1 h at 25°C and was then quenched with H_2O (15 mL). It was extracted with CH_2Cl_2 (2 x 15 mL). The aqueous layer was treated with 1N NaOH (15 mL), and extracted further with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with H_2O (25 mL) then brine (25 mL), dried, and evaporated to give the crude solid product which was dried in vacuo over P_2O_5 (0.94 g). This was taken up in a minimum of CH_2Cl_2 and loaded onto a 3 cm OD column packed with 6 in SiO_2 . Elution with CH_2Cl_2 and work up gave the pure product as a white crystalline solid (0.269 g, 21%), mp 196-197°C, and slightly less pure solid product (0.132 g, 10%), NMR ($\text{Me}_2\text{SO}-d_6$) δ 4.46 (s, 2H, CH_2), 7.38 (dd, 1H, H^3), 7.59-7.69 (m, 6H), 7.89-7.95 (m, 5H), 11.17 (s, 1H, NH). Anal. ($\text{C}_{22}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_3\text{S}_2 \cdot 1.1\text{H}_2\text{O}$) C, H, N, S; Cl: calcd, 19.49; found, 20.62, 20.59.

Preparation of Compound (121) --

2-Amino-5-((4-phenylsulfonyl)benzyl)thio)benzonitrile

NH_3 gas was bubbled for about 1 min through a solution of the anilide 120 (269 mg, 0.51 mmol) in MeOH (30 mL). The solution, which became warm to the touch, was stirred at 25°C for 5.5 days. It was then treated with 1N NaOH (25 mL) to precipitate a yellow solid. The mixture was poured into H_2O (75 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated to give a crude yellow solid (169 mg, 87%) suitable for further use. Flash chromatography of a small portion using 50% EtOAc in hexane gave the analytical sample as a white solid, mp 176-177°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 4.08 (s, 2H, CH_2), 6.25 (br s, 2H, NH_2), 6.65 (d, 1H, $J = 8.7$ Hz, H^3), 7.17 (dd, 1H, $J = 2.2, 8.7$ Hz, H^4), 7.32 (d, 1H, $J = 2.2$ Hz,

H⁶), 7.40 (d, 2H, J = 8.4 Hz, aromatic), 7.62-7.69 (m, 3H, aromatic), 7.85 (d, 2H, J = 8.4 Hz, aromatic), 7.91 (d, 2H, J = 8.4 Hz, aromatic). Anal. (C₂₀H₁₆N₂O₂S₂) C, H, N, S.

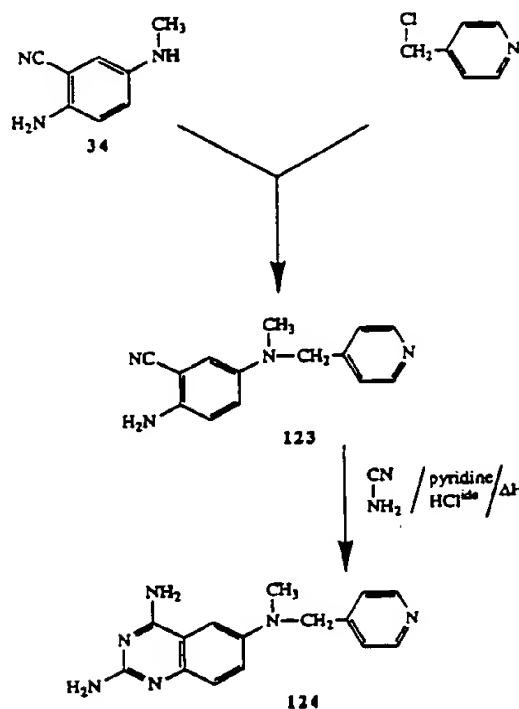
Preparation of Compound (122) --
2,4-Diamino-6-((4-(phenylsulfonyl)
benzyl)thio)quinazoline

A mixture of the technical quality aminonitrile 121 (139 mg, <0.365 mmol), pyridine hydrochloride (253 mg, 2.19 mmol, 6 eq), and cyanamide (61 mg, 1.46 mmol, 4 eq) was homogenized with a glass rod in a 25 mL round bottom flask, which was then immersed in a 165°C oil bath for 5 min. A melt resulted which was cooled to room temperature, whereupon it became a sludge. EtOH (7mL) was added, and the mixture was heated to boiling while being worked with a glass rod. Et₃N (0.41 mL, 2.92 mmol, 8 eq) was next added, and the mixture boiled further. A yellow precipitate formed. The mixture was cooled and put on ice. The precipitate was filtered off, washed with EtOH (10 mL) followed by Et₂O (10 mL), and dried over P₂O₅ in vacuo (21 mg). Meanwhile, most of the solvent in the filtrate had evaporated to leave behind a thick liquid containing a few crystals. Et₂O (2 mL) and EtOH (1 mL) were added to precipitate a paler yellow solid. The mixture was put on ice for 30 min, and the precipitate was then filtered off, washed with Et₂O (20 mL), and dried over P₂O₅ in vacuo (205 mg). NMR showed that the second solid was replete with Et₃N; it was therefore suspended in H₂O (2 mL), filtered off, washed with EtOH (1 mL) followed by Et₂O (2 mL), and dried over P₂O₅ in vacuo (31 mg, >20%). The final product was a light yellow powder, mp 247-249°C with darkening at 157°C, softening at 176°C, and gas evolution at 242°C. NMR (Me₂SO-d₆) δ 4.37 (s, 2H, CH₂), 7.28 (d, 3H, J = 8.7 Hz, H⁸ & NH₂), 7.57 - 7.68 (m, 6H, H⁷ & aromatic), 7.86 (d, 2H, J = 8.3 Hz, aromatic), 7.91 (d, 2H, J = 8.5 Hz, aromatic), 8.15 (d, 1H, J = 1.4 Hz, H⁵), 8.28 (br s, 2H, NH₂). Anal. (C₂₁H₁₈N₄O₂S₂ · 0.68H₂O) C, H, N; S: calcd, 14.75; found, 14.18. HRMS, FAB:

thioglycerol/glycerol (1/1) matrix, $(C_{21}H_{19}N_4O_2S_2)^+$ calcd, 423.0949; found, 423.0956.

Example 18: Preparation of Compound 124

Compound 124 was prepared according to the following reaction scheme:



**Preparation of Compound (123) --
2-Amino-5-(N-((4-pyridyl)methyl)
methylamino)benzonitrile**

A solution of 4-(chloromethyl)pyridine hydrochloride (2.46 g, 15 mmol), 2-amino-5-(methylamino)benzonitrile (2.21 g, 15 mmol), and Et_3N (4.6 mL, 33 mmol, 2.2 eq) in DMA (30 mL) was stirred at 90°C under argon for 2 h 10 min, at which time further of the pyridine (2.46 g, 15 mmol) and Et_3N (2.3 mL, 16.5 mmol) were added. At 3 h 15 min, the mixture was cooled and poured into H_2O (200 mL) and extracted with EtOAc (4 x 50 mL). The combined extracts were dried, treated with

charcoal, and evaporated to give a viscous brown oil which was flash chromatographed on SiO_2 (150 g) using EtOAc to give the product as a dark, orange-colored oil suitable for further use (1.62 g, 45%). A pure fraction was evaporated separately to give the analytical sample as an orange-colored oil, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.85 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 5.35 (s, 2H, NH_2), 6.68 (d, 1H, $J = 3.0$ Hz, H^6), 6.71 (d, 1H, $J = 9.1$ Hz, H^3), 6.94 (dd, 1H, $J = 9.1, 3.0$ Hz, H^4), 7.18 (d, 2H, $J = 6.0$ Hz, $\beta\beta'$), 8.47 (d, 2H, $J = 6.0$ Hz, $\alpha\alpha'$).
Anal. ($\text{C}_{14}\text{H}_{14}\text{N}_4 \cdot 0.3\text{H}_2\text{O}$) C, H, N.

Preparation of Compound (124) --

2,4-Diamino-6-(N-((4-pyridyl)methyl)
methylamino)quinazoline

A mixture of the aminonitrile 123 (1.62 g, 6.8 mmol), pyridine hydrochloride (4.71 g, 40.8 mmol, 6 eq), and cyanamide (1.14 g, 27.2 mmol, 4 eq) was heated at about 150°C for 22 min to give a dark red melt which was dissolved in boiling EtOH (25 mL) and treated with Et_3N . The resulting solution was poured into H_2O (200 mL) and extracted with EtOAc (3 x 50 mL). The extracts were combined, dried, charcoal treated, and evaporated to give an orange-colored solid which, slurried in DMF (0.5 mL), was treated with MeOH (10 mL), filtered, and washed with MeOH (10 mL) to give the pure product as an orange-colored powder (0.18 g, 9.2%), mp $285-287^\circ\text{C}$ dec, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.97 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.62 (s, 2H, NH_2), 7.08-7.18 (m, 5H, H^5 , H^7 , H^8 & NH_2), 7.21 (d, 2H, $J = 6.0$ Hz, $\beta\beta'$), 8.47 (d, 2H, $J = 6.0$ Hz, $\alpha\alpha'$). Anal. ($\text{C}_{15}\text{H}_{16}\text{N}_6 \cdot 0.2\text{H}_2\text{O}$) C, H, N. HRMS, DCI ($\text{C}_{15}\text{H}_{17}\text{N}_6$)⁺ calcd, 281.1515; found, 281.1515 (sic).

Cyclization of Aminobenzonitriles with Cyanamide

The method used is that described by A. Rosowsky [*J. Org. Chem.* 31 2607 (1966)]. Examples of this process have already been described for compounds 64, 105, 116, 122, and 124.

Each diaminoquinazoline was prepared by heating a mixture of the corresponding aminobenzonitrile (1 mol eq), cyanamide (4 mol eq),* and pyridine hydrochloride (6 mol eq)

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at 160-165° for the specified time. A melt was obtained which usually resolidified while still hot or which at least gave a solid upon cooling. Work up involved treatment with Et₃N (8 mol eq)^S. Except where stated, yields refer to isolated, pure product.

| Compound | Substituent | Substrate # (mmol) | Rxn time (min) | Yield (%) | |
|----------|------------------------|-----------------------|-------------------|--------------|-----------------|
| 46 | 4'-OMe | 45 | 5.4 | 5 | 40 |
| 48 | 4'-OH | 47 | 5.1 | 30 | 19 |
| 60 | SO ₂ -morph | 59 | 4.1 | 15 | 26 |
| 6 | cyano | 67 | 6.2 | 7 | 50 |
| 39 | nitro | 38 | 5.0 | 3 | 65 ⁺ |

*1.3 eq for the preparation of the cyano compound 6.

^SNo Et₃N was used for the phenolic compound 48.

⁺Technical quality product.

Isolation

46: The reaction mixture was slurried in boiling EtOH (30 mL), treated with Et₃N, and cooled in ice for 10 min. The resulting orange-colored solid was filtered, washed with EtOH (30 mL), then with Et₂O (30 mL), dissolved in boiling MeOH (150 mL), charcoal treated, and hot filtered. When the filtrate had cooled, Et₂O (200 mL) was added to precipitate the pure product (0.77 g) which was filtered off and washed with 1:1 Et₂O:MeOH (100 mL), followed by Et₂O (100 mL). Concentration of the mother liquor followed by addition of Et₂O (150 mL) afforded further pure product (0.214 g).

48: The reaction mixture was dissolved in boiling MeOH (150 mL), charcoal treated, and poured into saturated brine (500 mL). The resulting crude, yellow, flocculent solid was filtered off and washed with H₂O (75 mL). The solid was dissolved in DMF (25 mL), coated onto SiO₂ (10 g) and chromatographed on SiO₂ (200 g) with 5% Et₃N/20% MeOH/75% CH₂Cl₂ as eluant to give the pure product as a yellow solid (0.359 g). The column was washed with MeOH (1 L) to give an eluate that was evaporated to give a brown residue which was

chromatographed twice on SiO_2 using the above eluant to give additional pure product (63 mg).

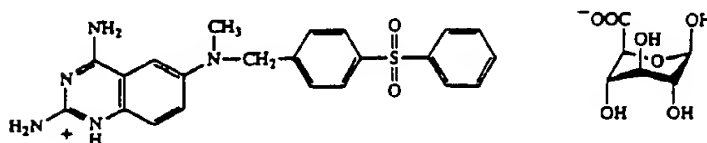
60: The reaction mixture was slurried in boiling EtOH (25 mL), treated with Et_3N , and cooled in ice. The crude solid was filtered off, washed sequentially with EtOH (2 x 10 mL), CH_2Cl_2 (10 mL), and Et_2O (2 x 15 mL), dissolved in DMSO (20 mL), coated onto basic alumina (10 g), and chromatographed on basic alumina (100 g) using 10% MeOH in CH_2Cl_2 as eluant to give the pure product as an orange-colored solid (0.245 g). The column was washed with MeOH (500 mL) to give an eluate which was charcoal treated, and evaporated to give an orange-colored solid. This was collected and washed with MeOH (10 mL) and then Et_2O (25 mL), and dried to afford further pure product (0.230 g).

6: The reaction mixture was slurried in hot 90% EtOH (30 mL), treated with Et_3N , and cooled in ice for 20 min. The resulting solid was filtered, washed with EtOH (2 x 25 mL) then Et_2O (2 x 25 mL). The crude product was dissolved in DMSO (25 mL), coated onto basic alumina (20 g), and chromatographed on basic alumina (250 g) with 10-25% MeOH in CH_2Cl_2 as eluant to give the pure, flesh-colored solid product (0.96 g).

39: The reaction mixture was slurried in boiling EtOH (25 mL), treated with Et_3N and allowed to cool to 25°C. The crude, technical-quality, light orange-colored solid product was filtered off and washed sequentially with EtOH (3 x 20 mL) and Et_2O (25 mL), (1.50 g).

The NMR spectrum ($\text{Me}_2\text{SO}-d_6$) of each quinazoline product satisfied identity and purity.

Preparation of Compound (125) --
2,4-Diamino-6-(N-(4-(phenylsulfonyl)benzyl)
methylamino)quinazoline glucuronate



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Glucuronic acid (32.8 g, 169 mmol, 5 eq) was dissolved in boiling MeOH (1 L), and to it was added 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline (22, 14.2 g, 33.8 mmol). The resulting solution was immediately hot filtered to remove traces of entrained matter, and the filtrate was boiled for 10 min to reduce its volume to about 820 mL, whereupon the first trace of product, a fluffy solid, started to appear. The mixture was removed from heat, cooled slowly, and kept for 10 days at 25°C to fully crystallize. The glucuronate, a yellow flocculent solid, was filtered off, washed with cold MeOH (2 x 100 mL) and dried in a desiccator (17.12 g, 82%), mp 203°C dec, NMR ($\text{Me}_2\text{SO}-d_6$) satisfactory. Anal. ($\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_9\text{S} \cdot 2.2 \text{ H}_2\text{O}$) C, H, N, S.

Synthesis of Glucuronate Salts

Glucuronate salts were prepared by dissolving glucuronic acid (5 mol eq) in boiling MeOH to give a solution to which was added the free base (1 mol eq). The resulting hot solution was immediately filtered to remove trace particulate matter, and the filtrate was allowed to cool to room temperature and held thus for the time stated before workup.

The glucuronate 130 was prepared by dissolving the glucuronic acid (5 eq) in boiling MeOH followed by filtration, since during the addition and dissolution of the free base the glucuronate salt spontaneously appeared.

All glucuronates were yellow solids which were collected by filtration and washed sequentially with ice-cold MeOH, 1:1 $\text{Et}_2\text{O}/\text{MeOH}$, and finally Et_2O . The glucuronates 128 and 131 had not appeared after standing at room temperature overnight

(16 h) and were thus precipitated with Et₂O (25 mL), filtered off, and washed with Et₂O (10 mL). Additional amounts of glucuronates 128 (16 mg), 126 (50 mg), 131 (45 mg), and 127 (15 mg) were obtained by adding Et₂O (25-30 mL) to the respective mother liquors and collecting the solid which resulted. Similarly, the glucuronate 134 was precipitated with Et₂O (450 mL), collected, and washed with Et₂O (250 mL). The filtrate was evaporated down to a volume of 200 mL, and Et₂O (200 mL) was added to precipitate a second crop which was collected and washed with Et₂O (150 mL). Upon standing overnight, the second filtrate deposited a third crop which was filtered off and washed with Et₂O (100 mL). In the case of the glucuronate 135, the reaction volume was reduced to 10 mL before cooling, Et₂O (15 mL) was then added to precipitate the product which was collected and washed with 50% MeOH in Et₂O (10 mL) and then Et₂O (25 mL). All glucuronates had satisfactory NMR spectra. The glucuronate 134, chosen to represent the series, gave a satisfactory mass spectrum - HRMS, FAB: nitrobenzyl alcohol matrix, (C₃₂H₃₄N₅O₉S)⁺ calcd, 664.2077; found, 664.2069.

| Glucuronate # structure | Free base # (mg) | MeOH (mL) | Time at RT (h) | Yield (%) | mp (dec) (°C) |
|----------------------------|---------------------|--------------|-------------------|--------------|------------------|
| 126 CN | 6 210 | 30 | 2.5 | 70.6 | 189 |
| 127 NH ₂ | 40 210 | 20 | 16 | 42.4 | 200 |
| 128 OH | 48 210 | 20 | 16 | 63 | 89 |
| 129 N(Me) ₂ | 54 210 | 30 | 2.5 | 52.4 | 217 |
| 130 morph | 60 210 | 25 | 2.5 | 88.5 | 168 |
| 131 F | 64 210 | 20 | 16 | 67 | 86 |
| 132 SCH ₃ | 65 140 | 20 | 16 | 67.7 | 177 |
| 133 NO ₂ | 39 500 | 60* | 2 | 54 | 179 |
| 134 α-naph | 87 4270 | 500 | 16 | 57.6 | 157 |
| 135 N ⁹ -ethyl | 105 100 | 20 | 1.5 | 76.5 | 112 |

*Volume reduced by evaporation to 40 mL before cooling.

| Glucuronate | Formula | Analysis |
|-------------------------|---|-----------|
| 126 CN | $C_{23}H_{26}N_6O_7 \cdot 1.6 H_2O$ | C,H,N,S |
| 127 NH ₂ | $C_{28}H_{32}N_6O_9S \cdot 0.5C_6H_{10}O_7 \cdot 1.1 H_2O$ | C,H,N,S* |
| 128 OH | $C_{28}H_{31}N_5O_{10}S \cdot 0.76C_6H_{10}O_7 \cdot 0.38Et_2O \cdot 0.5H_2O$ | C,H,N,S* |
| 129 N(Me ₂) | $C_{24}H_{32}N_6O_9S \cdot 1.4 H_2O$ | C,H,N,S |
| 130 morph | $C_{26}H_{34}N_6O_{10}S$ | C,H,N,S |
| 131 F | $C_{28}H_{30}FN_5O_9S \cdot 0.6C_6H_{10}O_7 \cdot 0.17Et_2O \cdot 0.85H_2O$ | C,H,N,S, |
| 132 SMe | $C_{29}H_{33}N_5O_9S_2 \cdot 0.8 H_2O$ | C,H,N,S |
| 133 NO ₂ | $C_{28}H_{30}N_6O_{11}S \cdot 0.2 Et_2O \cdot 0.9 H_2O$ | C,H,N,S* |
| 134 α -naph | $C_{32}H_{33}N_5O_9S \cdot 0.21 H_2O$ | C,H,S;N*† |
| 135 N ⁹ -Et | $C_{29}H_{33}N_5O_9S \cdot 0.74 C_6H_{10}O_7 \cdot 0.76 H_2O$ | C,H,N;S*§ |

* The presence of additional glucuronic acid, and ether, was confirmed by NMR.

† N: calcd, 10.49; found, 11.10.

§ S: calcd, 4.08; found, 3.37.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Determination of Inhibition Constants Against 5,10-Methylene-tetrahydrofolate for the Enzyme Thymidylate Synthase

Thymidylate synthase activity was measured using a modification of the tritium release method of Lomax and Greenberg [M.I.S. Lomax and G.R. Greenberg, *J. Biol. Chem.* 242 109 (1967)]. Inhibition constants, K_i , slope and K_i , intercept [W.W. Cleland, *Biochim. Biophys. Acta* 67 173 (1963)], were determined against the cofactor (6R, 6S)-5,10-methylene-tetrahydrofolate which was generated *in situ* by reaction of tetrahydrofolate with formaldehyde [R.G. Kallen and W.P. Jencks, *J. Biol. Chem.* 241 5851 (1966)]. The cofactor was present as the variable substrate under conditions of saturating radiolabelled 2'-deoxyuridine 5'-monophosphate (dUMP). Assays in a total volume of 0.1 mL contained 50mM Tris @ pH 7.6, 10mM DTT (dithiothreitol), 1mM EDTA (ethylenediaminetetraacetic acid), 25mM MgCl₂, 15mM formaldehyde, \pm 1% DMSO (depending on the solubility of the compound), 25 μ M [5-³H] dUMP (specific activity 2×10^8 cpm/ μ mol), tetrahydrofolate (eight concentrations ranging from

5 μ M to 300 μ M) and enzyme (=30 ng for *E. coli* TS and =60 ng for human TS). Assays of human TS also contained 1-5 μ g/mL bovine serum albumin to stabilize the protein. Reactions were initiated by the addition of enzyme and were carried out for 5 minutes at 24°C, and then quenched by the addition of charcoal (15 mg in 0.1 mL H₂O). The quenched samples were centrifuged at 10,000 rpm for 12-15 min at 40°C to remove unreacted dUMP which had bound to the charcoal, and 0.1 mL of the supernatant was counted by liquid scintillation in the presence of 5 mL ecolume to determine the release of tritium label from the 5-position of the dUMP. A standard curve was established in the absence of inhibitor, and three additional curves containing inhibitor at approximately 1/2 to 2 times the K_i were determined. Experimental results were analyzed by EZ-FIT, a nonlinear regression analysis program (Perrella Scientific, Springfield, PA) which was used to fit all data points simultaneously to a mixed noncompetitive inhibition scheme. The results obtained are shown in the Table. The first entry for each compound is the K_i , slope and the entry underneath is the K_i , intercept.

Determination of Inhibition Constants Against

7,8-Dihydrofolate for the Enzyme

Dihydrofolate Reductase

Dihydrofolate reductase (DHFR) inhibition constants were determined using purified human recombinant enzyme at 25°C. All reaction mixtures contained 50 μ M Tris at pH 7.5, 60 μ M NADPH (nicotinamide adenine dinucleotide, reduced form). Reaction mixtures, containing DHFR, were preincubated for 2 min in the presence of inhibitor before initiation by addition of dihydrofolate (DHF). The initial reaction concentration of DHF was 50 μ M(s). The assays were done on a spectrophotometer at 340 nm, following the decrease in DHF [M.S. Lui, R.C. Jackson, and G. Weber, *Biochem. Pharmacol.* 28 1189 (1975); mM extinction coefficient of DHF = 6.4]. A time course was monitored for each inhibitor concentration to determine the maximum steady state reaction rate after equilibration. Rate measurements for at least eight

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inhibitor concentrations were used in each K_i determination. Initial estimates of inhibition constants, $K_{i, app}$, were computed by non-linear regression fit to the equation of Morrison [Biochim, Biophys. Acta 185 269 (1969)]. $K_{i, slope}$ was calculated as:

$$K_{i, slope} = K_{i, app} / (1 + s/K_m)$$

where $s = 50 \times 10^{-6} M$, as stated. The K_m for DHF was $21 \times 10^{-9} M$ for this DHFR preparation. The results obtained are shown below in the Table.

In Vitro Testing to Determine Inhibition of Growth of Tumor Cells

Cellular growth in the presence of the compounds in question was assessed using three cell lines: the L1210 murine leukemia (ATCC CCL 219), CCRF-CEM, a human lymphoblastic leukemia line of T-cell origin (ATCC CCL 119), and a thymidine kinase-deficient human colon adenocarcinoma, GC₃/M TK⁻ (supplied by Drs. P.J. and J.A. Houghton, St. Jude Childrens Research Hospital, Memphis, TN). Cell lines were maintained in RPMI 1640 medium containing 5% (L1210, CCRF-CEM) or 10% (GC₃/M TK⁻) heat-inactivated fetal bovine serum without antibiotics.

IC₅₀ values were determined in 150 μL microcultures each containing 1500 (L1210) or 10,000 (CCRF-CEM, GC₃/M TK⁻) cells established in 96 well plates in growth medium supplemented with 50 U/mL penicillin and 50 $\mu g/mL$ streptomycin. Growth was measured over 3 days (L1210) or 5 days (CCRF-CEM, GC₃/M TK⁻) of continuous exposure to varying concentrations of each test compound, added 4 h. after initial cell plating, by the MTT-tetrazolium reduction assay of T.J. Mosmann [J. Immunol. Meth. 65 55 (1983)] modified according to Alley et al. [Cancer Res. 48 589 (1988)]. Water insoluble derivatives were dissolved in DMSO and diluted to a final concentration of 0.5% solvent in cell cultures.

The results obtained from this procedure are shown below in the Table.

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TABLE

| Compound # Descriptor | <u>K_i for TS (μM)</u> | | <u>K_i for</u> Human DHFR (pM) | <u>IC50 for Cells in Culture (μM)</u> | | |
|--------------------------|----------------------------------|----------------------------|---|---------------------------------------|----------|-----------------------|
| | E. coli | Human | | L1210 | CCRF/CEM | GC ₃ /M TK |
| 5 NH-cyano | 40±2 57±10 | 2.0±0.8 1.7±0.1 | 1550 | 0.27 | 1.7 | 7.1 |
| 6 cyano | 5.9±2.8 4.6±2.2 | 0.24±0.16 0.12±0.04 | 11 | 0.004 | 0.026 | 0.068 |
| 12 4-SMe | >10 >10 | 23±4 25±8 | >5,000 | 2.05 | 3.5 | >5.0 |
| 16 4-MeNH | 33±4 49±19 | 0.97±0.52 0.36±0.16 | 5,000 | 1.4 | 3.4 | 10.0 |
| 22 4'-H | 13±0.3 1.2±0.3 | 0.089±0.038 0.033±0.005 | 20 | 0.0035 | 0.016 | 0.039 |
| 30 4'-NH-OH | 9.2±0.3 21±4 | 0.21±0.08 0.31±0.04 | >10,000 | 0.043 | 1.0 | 2.0 |
| 31 4'-NH-NH ₂ | 10±2 14±3 | 0.99±0.16 0.70±0.22 | 46 | 0.009 | 0.17 | 0.7 |
| 39 4'-Nitro | 1.6±0.5 2.2±0.1 | 0.054±0.008 0.069±0.03 | 14 | 0.00085 | 0.0031 | 0.004 |

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| | | | | | | | |
|----|-----------------------------------|-----------|-------------|------|--------|--------|--------|
| 40 | 4'-Amino | 0.43±0.01 | 0.025±0.004 | 13 | 0.004 | 0.014 | 0.021 |
| | | 0.43±0.1 | 0.026±0.009 | | | | |
| 46 | 4'-OMe | 1.2±0.1 | 0.047±0.009 | 13 | 0.0017 | 0.0048 | 0.0088 |
| | | 1.4±0 | 0.051±0.008 | | | | |
| 48 | 4'-OH | 0.41±0.04 | 0.019±0.007 | 9 | 0.0035 | 0.055 | 0.095 |
| | | 0.50±0.07 | 0.012±0.003 | | | | |
| 54 | SO ₂ -NMe ₂ | 7.2±1.6 | 0.10±0.04 | 28 | 0.0033 | 0.011 | 0.022 |
| | | 5.5±0.4 | 0.18±0.04 | | | | |
| 60 | SO ₂ morph | 2.3±0.4 | 0.12±0.02 | 7.2 | 0.0023 | 0.011 | 0.02 |
| | | 1.7±0.2 | 0.082±0.018 | | | | |
| 64 | 4'-F | 2.5±0.5 | 0.13±0.01 | 0.73 | 0.0008 | 0.009 | 0.018 |
| | | 2.6±0.4 | 0.081±0.003 | | | | |
| 65 | 4'-SMe | 3.0±0.4 | 0.17±0.02 | 0.77 | 0.0005 | 0.0065 | 0.009 |
| | | 5.5±0.6 | 0.22±0.01 | | | | |
| 73 | Br-Indole | >1 | 0.81±0.19 | ~150 | 0.043 | 0.16 | 0.95 |
| | | >1 | 0.36±0.1 | | | | |
| 81 | Indole | 22±5 | 0.45±0.3 | 48 | 0.01 | 1.2 | 0.29 |
| | | 22±6 | 0.13±0.02 | | | | |
| 87 | -Naphth | 3.7±0.9 | 0.25±0.14 | 22 | 0.007 | 0.029 | 0.07 |
| | | 5.7±0.8 | 0.27±0.11 | | | | |
| 93 | -Naphth | 2.9±1.6 | 0.30±0.12 | 38 | 0.0028 | 0.0045 | 0.015 |
| | | 7.0±4.1 | 0.27±0.1 | | | | |

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| | | | | | | | |
|-----|-----------------------|-----------|-------------|------|-----------|--------|--------|
| 98 | 2-MeS | >1 | >1 | N.D. | 3.9 | 1.8 | >5.0 |
| | | >1 | >1 | | | | |
| 99 | 2,4-hydraz | | | | Insoluble | | |
| 100 | 2,4-MeNH | | 0.51±0.03 | \$ | 0.9 | 1.05 | 2.8 |
| | | | 1.2±0.2 | | | | |
| 101 | 2-MeNH | | 0.49±0.19 | 1000 | 0.1 | 1.0 | 5.0 |
| | | | 0.48±0.29 | | | | |
| 105 | N ⁹ -Ethyl | 0.48 | 0.041±0.012 | 0.29 | 0.0004 | 0.004 | 0.0041 |
| | | 0.31 | 0.051±0.006 | | | | |
| 116 | CH ₂ S | | 0.99 | 8.2 | 0.09 | 1.0 | 1.5 |
| | | | 0.77 | | | | |
| 122 | SCH ₂ | | | \$ | 0.8 | >10 | >10 |
| 124 | picolyl | | 0.29 | 170 | 0.0031 | 0.105 | 0.15 |
| | | | 0.23 | | | | |
| 125 | 4'-H Gluc | 1.7±0.5 | 0.068±0.001 | 13 | 0.0039 | 0.0103 | 0.023 |
| | | 0.86±0.08 | 0.044±0.006 | | | | |
| 126 | cysano Gluc | | 0.17±0.03 | N.D. | 0.0021 | 0.029 | 0.072 |
| | | | 0.15±0.03 | | | | |
| 127 | NH ₂ Gluc | | 0.022±0.004 | N.D. | 0.0105 | 0.061 | 0.24 |
| | | | 0.033±0.004 | | | | |
| 128 | OH Gluc | | 0.026±0.004 | N.D. | 0.0023 | 0.03 | 0.14 |
| | | | 0.018±0.001 | | | | |

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| | | | | | | |
|-----|----------------------------------|-------------|------|--------|-------|--------|
| 129 | SO ₂ NMe ₂ | 0.13±0 | N.D. | 0.0021 | 0.01 | 0.04 |
| | Gluc | 0.16±0.01 | | | | |
| 130 | SO ₂ -morph | 0.068±0.002 | 5.7 | 0.0031 | 0.021 | 0.059 |
| | Gluc | 0.081±0.009 | | | | |
| 131 | 4'-F Gluc | 0.14±0.06 | N.D. | 0.0014 | 0.013 | 0.037 |
| | | 0.059±0.001 | | | | |
| 132 | 4'-SMe | 0.070±0.011 | N.D. | 0.0012 | 0.005 | 0.0195 |
| | Gluc | 0.095±0.003 | | | | |
| 133 | NO ₂ Gluc | | N.D. | <0.001 | N.D. | N.D. |
| | | | | | | |
| 134 | α-Naph | | N.D. | 0.0009 | 0.03 | >0.05 |
| | Gluc | | | | | |

N.D. = Not determined

§ = No inhibition observed at a drug concentration of 5 M (limit of solubility in the experiment)

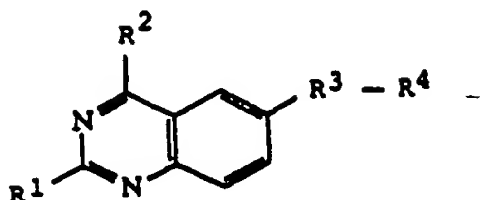
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While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof. Thus, it is intended that the present invention cover the modifications and variations provided they come within the scope of the appended claims and their equivalents.

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WE CLAIM:

1. A quinazoline compound having the formula I



I

wherein:

R^1 and R^2 , which may be the same or different, represent electron-donating substituents;

R^3 represents a $-S-CH_2-$ group, a $-CH_2-S-$ group or a $-N(R^5)-CH_2-$ group, wherein R^5 is hydrogen, or a lower alkyl; and

R^4 represents a substituted or unsubstituted aryl or heteroaryl group;

provided that, when R^1 and R^2 both represent $-NH_2$, R^4 does not represent (a) an unsubstituted phenyl; (b) an unsubstituted naphthyl; (c) a substituted phenyl selected from the group consisting of mono-, di- or tri-(lower alkyl)phenyl, mono- or di- halo phenyl, hydroxyphenyl, mono-, di- or tri-(lower alkoxy)phenyl, carboxyphenyl, carb-(lower alkoxy)phenyl, nitrophenyl, aminophenyl, mono- or di-(lower alkyl) aminophenyl, and acetamidophenyl; (d) a phenyl substituted in the para-position with any of the following groups: $-CO-NHR_b$ where R_b is such that NH_2-R_b is an amino acid, a poly(amino acid), a lower alkyl ester of an amino acid, or a lower alkyl ester of a poly(amino acid); (e) a substituted naphthyl selected from the group consisting of halonaphthyl, hydroxynaphthyl, nitronaphthyl, aminonaphthyl and lower alkoxy naphthyl; or (f) an unsubstituted furyl, thienyl or pyridyl group.

2. A compound according to claim 1, wherein said electron-donating substituents R^1 and R^2 are selected from the group consisting of $-NH_2$, $-NH-(\text{lower alkyl})$, $-NHOH$, $-NHNH_2$, $-S-(\text{lower alkyl})$ and $-NR_6R_7$, wherein R_6 and R_7 represent lower alkyl groups.

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3. A compound according to claim 2, wherein at least one of R^1 and R^2 is $-NH_2$.

4. A compound according to claim 3, wherein both R^1 and R^2 are $-NH_2$.

5. A compound according to claim 1, wherein R^3 is a $-N(R^5)-CH_2-$ group, wherein R^5 is a lower alkyl.

6. A compound according to claim 5, wherein R^5 is a $-CH_3$ group.

7. A compound according to claim 1, wherein said substituted or unsubstituted aryl or heteroaryl group R^4 is mono- or bi- cyclic.

8. A compound according to claim 7, wherein R^4 represents phenyl substituted by a $-SO_2-R^8$ group, wherein R^8 represents an aryl or heteroaryl group.

9. A compound according to claim 8, wherein R^8 represents a morpholino group, a dimethylamino group, a naphthyl group, a substituted or unsubstituted indole, an unsubstituted phenyl group or a phenyl group substituted by a radical selected from the group consisting of lower alkoxy, amino, (lower alkyl)-amino, nitro, hydroxy, carboxy, halo, and (lower alkyl)-thio.

10. A compound according to claim 7, wherein R^4 represents a phenyl substituted by a cyano group.

11. The compound of claim 1, wherein said compound has a thymidylate synthase inhibition constant K_i of less than or equal to about $10^{-6}M$.

12. The compound of claim 1, wherein said compound has a human DHFR inhibition constant K_i of less than or equal to about $10^{-6}M$.

13. A process of making a compound of the formula I according to claim 1, wherein R^1-R^4 have the same meanings as claimed in claim 1, comprising the steps of:

(1) reacting a compound $L - CH_2 - R^4$ with a (lower alkyl)-amine, wherein L is a leaving group, and R^4 has the same meaning as claimed in claim 1;

(2) reacting the product of step (1) with 5-chloro-2-nitrobenzonitrile to form a nitro containing intermediate;

(3) reducing the nitro group of the intermediate of step (2); and

(4) reacting the product of step (3) with a cyclization reagent.

14. A process of making a compound according to claim 13, wherein step (1) is carried out in the presence of a base at a temperature of from 0°C to about 100°C.

15. A process of making a compound according to claim 13, wherein step (1) is carried out with an excess of the amine at a temperature of from 0°C to about 100°C.

16. A process of making a compound according to claim 13, wherein step (2) is carried out in the presence of a base at a temperature of from room temperature to about 189°C.

17. A process of making a compound according to claim 13, wherein step (3), is carried out in an organic solvent in the presence of either hydrogen gas under a vapor pressure of one atmosphere or higher or in the presence of a reducing agent at a temperature of from about room temperature to about 100°C.

18. A process of making a compound according to claim 13, wherein in step (4), the cyclization reagent is selected from the group consisting of chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithio carbiminium iodide and thiourea.

19. A process of making a compound according to claim 17, wherein thiourea is used as the cyclization reagent, and the resulting product is then further reacted with NaH, followed by iodomethane.

20. A process of making a compound of the formula I according to claim 1, wherein R^1 - R^4 have the same meanings as claimed in claim 1, comprising the steps of:

(1) reacting a compound $L - CH_2 - R^4$ with a 2-amino-5-(lower alkyl amino)benzonitrile, wherein L is a leaving group, and R^4 has the same meaning as claimed in claim 1; and

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(2) reacting the product of step (1) with a cyclization reagent.

21. A process of making a compound according to claim 20, wherein step (1) is carried out in the presence of a base at a temperature of from about room temperature to about 150°C.

22. A process of making a compound according to claim 20, wherein in step (2), the cyclization reagent is selected from the group consisting of chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide and thiourea.

23. A process of making a compound according to claim 20, wherein step (2) is carried out in the presence of an acid at a temperature of from about room temperature to about 200°C.

24. A process of making a compound according to claim 20, wherein thiourea is used as the cyclization reagent, and the resulting product is then further reacted with NaH, followed by iodomethane.

25. A process of making a compound of the formula I according to claim 1, wherein R^1 - R^4 have the same meanings as claimed in claim 1, comprising the steps of:

(1) reacting a compound $HS - R^4$ with a 5-(L-(lower alkyl)-2-((trifluoroacetyl)amino)benzonitrile, wherein L is a leaving group, and R^4 has the same meaning as claimed in claim 1;

(2) lysing the trifluoroacetyl group of the product of step (1); and

(3) reacting the product of step (2) with a cyclization reagent.

26. A process of making a compound according to claim 25, wherein step (1) is carried out in the presence of a base at a temperature of from about 0°C to about 100°C.

27. A process of making a compound according to claim 25, wherein step (2) is carried out in the presence of

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a lysing agent at a temperature of from about 0°C to about 100°C.

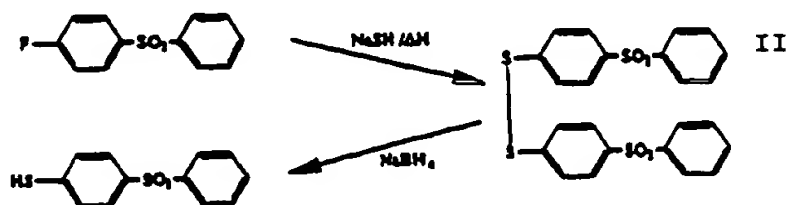
28. A process of making a compound according to claim 27, wherein said lysing agent is methanolic ammonia.

29. A process of making a compound according to claim 25, wherein in step (3), the cyclization reagent is selected from the group consisting of chloroformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide and thiourea.

30. A process of making a compound according to claim 25, wherein step (3) is carried out in the presence of an acid at a temperature of from about room temperature to about 200°C.

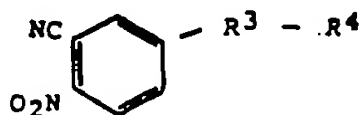
31. A process of making a compound according to claim 29, wherein thiourea is used as the cyclization reagent, and the resulting product is then further reacted with NaH, followed by iodomethane.

32. A process of making a compound according to claim 25, wherein the HS - R⁴ compound of step (1) is prepared by the following reaction scheme II:



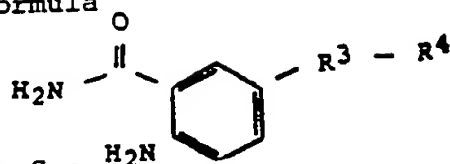
33. A process of making a compound of the formula I according to claim 1, wherein R³ is -S-CH₂- or -CH₂-S- and R¹, R₂ and R⁴ have the same meanings as claimed in claim 1, comprising the steps of:

(1) reacting a compound having the formula



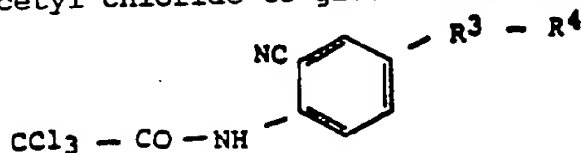
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wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$, with a reducing agent to give a compound having the formula



wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$;

(2) reacting the product of step (1) with trichloroacetyl chloride to give a compound having the formula



wherein R^3 is $-S-CH_2-$ or $-CH_2-S-$;

(3) lysing the trichloroacetyl group of the product of step (2); and

(4) reacting the product of step (3) with a cyclization reagent.

34. A process of making a compound according to claim 33, wherein step (1) is carried out in the presence of stannous chloride dihydrate in ethyl acetate or in ethanol at a temperature of from about 0°C to about 77°C .

35. A process of making a compound according to claim 33, wherein step (1) is carried out in the presence of a combination of stannous chloride dihydrate and sodium borohydride in ethanol at a temperature from about 0°C to about 78°C .

36. A process of making a compound according to claim 33, wherein step (1) is carried out in the presence of triiron dodecacarbonyl in a mixture of methanol and benzene at a temperature of from about room temperature to about 80°C .

37. A process of making a compound according to claim 33, wherein step (1) is carried out in the presence of hydrazine hydrate combined with graphite in ethanol at a temperature of from about 0°C to about 78°C .

38. A process of making a compound according to claim 33, wherein step (2) is carried out with an excess of

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the reagent in the presence of a base in an inert solvent at a temperature of from about 0°C to about 100°C.

39. A process of making a compound according to claim 33, wherein step (3) is carried out in the presence of methanolic ammonia at a temperature of from about 0°C to about 100°C.

40. A process of making a compound according to claim 33, wherein in step (4), the cyclization reagent is selected from the group consisting of chlorformamidine hydrochloride, cyanamide together with pyridine hydrochloride, S,S-dimethyldithiocarbiminium iodide and thiourea.

41. A process of making a compound according to claim 33, wherein step (4) is carried out in the presence of an acid at a temperature of from about room temperature to about 200°C.

42. A process of making a compound according to claim 40, wherein thiourea is used as the cyclization reagent and the resulting product is then further reacted with NaH, followed by iodomethane.

43. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in combination with an amount of a compound according to claim 1 effective to inhibit in a host in need of such treatment at least one folate metabolic pathway.

44. A pharmaceutical composition according to claim 43, in a form selected from the group consisting of forms suitable for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural and rectal administration.

45. A pharmaceutical composition according to claim 43, further comprising at least one other compound which is an antitumor agent.

46. A pharmaceutical composition according to claim 45, wherein said other compound is selected from the group consisting of mitotic inhibitors, alkylating agents, DHFR inhibitors, TS inhibitors, antimetabolites, intercalating

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antibiotics, enzymes, topoisomerase inhibitors or biological response modifiers.

47. A pharmaceutical composition according to claim 43, further comprising at least one other agent which is an antibacterial agent, an antifungal agent, an antiparasitic agent, an antiviral agent, an antipsoriatic agent, an antiprotozoal agent or an anticoccidial agent.

48. A pharmaceutical composition according to claim 46, further comprising at least one other agent which is an antibacterial agent, an antifungal agent, an antiparasitic agent, an antiviral agent, an antipsoriatic agent, an antiprotozoal agent or an anticoccidial agent.

49. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in combination with an amount of a compound according to claim 1 effective to inhibit the enzyme thymidylate synthase in a host in need of such treatment.

50. A pharmaceutical composition according to claim 49, wherein said compound has a thymidylate synthase inhibition constant K_i of less than or equal to about 10^{-4} M.

51. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in combination with an amount of a compound according to claim 1 effective to inhibit the enzyme dihydrofolate reductase in a host in need of such treatment.

52. A pharmaceutical composition according to claim 51, wherein said compound has a dihydrofolate reductase inhibition constant K_i of less than or equal to about 10^{-6} M.

53. A therapeutic process of inhibiting at least one folate metabolic pathway in a host in need of such treatment comprising administering to the host an amount of a compound according to claim 1 effective to inhibit at least one folate metabolic pathway in the host.

54. A therapeutic process according to claim 53, wherein the compound is in a form selected from the group consisting of forms suitable for oral, parenteral, topical,

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intravaginal, intranasal, intrabronchial, intraocular, intraaural and rectal administration.

55. A therapeutic process according to claim 53, wherein the compound is administered in a dose of up to about 1 gram per kilogram of the host.

56. A therapeutic process according to claim 53, wherein the host is a mammal.

57. A therapeutic process according to claim 53, wherein the host is a human.

58. A therapeutic process according to claim 53, wherein the host is a bird.

59. A therapeutic process according to claim 53, wherein the compound is further characterized as additionally producing an anti-proliferative effect not derived from the inhibition of a folate metabolic pathway.

60. A therapeutic process according to claim 53, wherein, prior to said process, the host harbors tumorous cells, and wherein the compound is characterized as producing an antitumor effect.

61. A therapeutic process according to claim 53, wherein the compound is further characterized as producing an effect selected from the group consisting of antibacterial, antifungal, antiparasitic, antiviral, antipsoriatic, antiprotozoal and anticoccidial effects.

62. A therapeutic process according to claim 53, wherein the compound is further characterized as producing an antifungal effect.

63. A therapeutic process of inhibiting thymidylate synthase in a host in need of such treatment, comprising administering to the host an amount of a compound according to claim 1 effective to inhibit thymidylate synthase.

64. A therapeutic process of inhibiting dihydrofolate reductase in a host in need of such treatment, comprising administering to the host an amount of a compound according to claim 1 effective to inhibit dihydrofolate reductase.

65. A therapeutic process of inhibiting both thymidylate synthase and dihydrofolate reductase in a host in

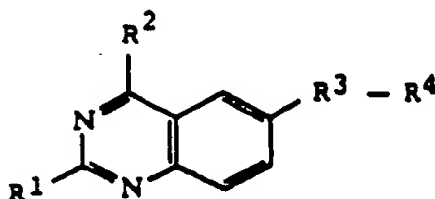
-132-

need of such treatment, comprising administering to the host
an amount of a compound according to claim 1 effective to
inhibit both thymidylate synthase and dihydrofolate
reductase.

AMENDED CLAIMS

[received by the International Bureau on 15 June 1993 (15.06.93);
original claim 59 deleted; original claims 1,2,3,7 and 55 amended;
remaining claims unchanged (3 pages)]

1. A quinazoline compound having the formula



I

wherein:

R^1 and R^2 , which may be the same or different, represent electron-donating substituents selected from $-NH_2$, $-NH$ -(lower alkyl), $-NHOH$, $-NHNH_2$, $-S$ -(lower alkyl) and $-NR^6R^7$, wherein R^6 and R^7 represent substituted or unsubstituted lower alkyl groups;

R^3 represents a $-S-CH_2-$ group, a $-CH_2-S-$ group or a $-N(R^5)-CH_2-$ group, wherein R^5 is hydrogen or a lower alkyl; and

R^4 represents an aryl or heteroaryl group substituted with a fluoroalkyl, cyano, carbamyl, carbonyl, amino acid sulfonyl, sulfamyl, sulfanilyl, sulfhydryl, sulfino, sulfinyl, sulfo, sulfonamido, sulfonyl, (lower alkyl)-thio, substituted or unsubstituted phenylsulfonyl, phenylmercapto, phosphazo, phosphinico, phosphino, phospho, phosphono, phosphoro, phosphoroso or mercaptoaryl group or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein at least one of R^1 and R^2 is $-NH_2$.

4. A compound according to claim 3, wherein both R^1 and R^2 are $-NH_2$.

5. A compound according to claim 1, wherein R^3 is a $-N(R^5)-CH_2-$ group, wherein R^5 is a lower alkyl.

6. A compound according to claim 5, wherein R^5 is a $-CH_3$ group.

7. A compound according to claim 1, wherein said aryl or heteroaryl group R^4 is mono- or bi- cyclic.

8. A compound according to claim 7, wherein R^4 represents phenyl substituted by a $-SO_2-R^8$ group, wherein R^8 represents an aryl or heteroaryl group.

9. A compound according to claim 8, wherein R^8 represents a morpholino group, a dimethylamino group, a naphthyl group, a substituted or unsubstituted indole, an unsubstituted phenyl group or a phenyl group substituted by a radical selected from the group consisting of lower alkoxy, amino, (lower alkyl)-amino, nitro, hydroxy, carboxy, halo, and (lower alkyl)-thio.

10. A compound according to claim 7, wherein R^4 represents a phenyl substituted by a cyano group.

11. The compound of claim 1, wherein said compound has a thymidylate synthase inhibition constant K_i of less than or equal to about $10^{-6}M$.

12. The compound of claim 1, wherein said compound has a human DHFR inhibition constant K_i of less than or equal to about $10^{-6}M$.

13. A process of making a compound of the formula I according to claim 1, wherein R^1-R^4 have the same meanings as claimed in claim 1, comprising the steps of:

(1) reacting a compound $L - CH_2 - R^4$ with a (lower alkyl)-amine, wherein L is a leaving group, and R^4 has the same meaning as claimed in claim 1;

(2) reacting the product of step (1) with 5-chloro-2-nitrobenzotrile to form a nitro containing intermediate;

intravaginal, intranasal, intrabronchial, intraocular, intraaural and rectal administration.

55. A therapeutic process according to claim 53, wherein the compound is administered in a daily dosage of up to about 1 gram per kilogram of the host.

56. A therapeutic process according to claim 53, wherein the host is a mammal.

57. A therapeutic process according to claim 53, wherein the host is a human.

58. A therapeutic process according to claim 53, wherein the host is a bird.

60. A therapeutic process according to claim 53, wherein, prior to said process, the host harbors tumorous cells, and wherein the compound is characterized as producing an antitumor effect.

61. A therapeutic process according to claim 53, wherein the compound is further characterized as producing an effect selected from the group consisting of antibacterial, antifungal, antiparasitic, antiviral, antipsoriatic, antiprotozoal and anticoccidial effects.

62. A therapeutic process according to claim 53, wherein the compound is further characterized as producing an antifungal effect.

63. A therapeutic process of inhibiting thymidylate synthase in a host in need of such treatment, comprising administering to the host an amount of a compound according to claim 1 effective to inhibit thymidylate synthase.

64. A therapeutic process of inhibiting dihydrofolate reductase in a host in need of such treatment, comprising administering to the host an amount of a compound according to claim 1 effective to inhibit dihydrofolate reductase.

65. A therapeutic process of inhibiting both thymidylate synthase and dihydrofolate reductase in a host in

INTERNATIONAL SEARCH REPORT

PCT/US 92/10730

International Application No

| | | |
|--|--|-------------------------------------|
| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC | | |
| Int.Cl. 5 | C07D239/78; C07D239/94; | A61K31/505; C07D401/14; |
| | C07D239/84; C07D403/14; | C07D239/86 C07D413/14 |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched ⁷ | | |
| Classification System | Classification Symbols | |
| Int.Cl. 5 | C07D ; A61K | |
| Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸ | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ | | |
| Category ¹⁰ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ |
| X | EP,A,0 373 891 (ICI) 20 June 1990 compounds (I) where R2 is alkyl or hydrogen and all such examples --- | 1-52 |
| X | US,A,4 857 530 (BERMAN) 15 August 1989 compounds (I) where R is hydrogen and R2 is alkyl and examples thereof. --- -/-- | 1-52 |
| ¹⁰ Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | |
| 23 MARCH 1993 | 21. 04. 93 | |
| International Searching Authority | Signature of Authorized Officer | |
| EUROPEAN PATENT OFFICE | GETTINS M.P. | |

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|--|-----------------------|
| Category ^a | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
| X | CHEMICAL ABSTRACTS, vol. 98, no. 21, 23 May 1983, Columbus, Ohio, US; abstract no. 179317g, LI 'Studies on antimalarials.' page 654 ;column 2 ; see abstract Formula II and CN85628-86-0 and CNs starting with 85609 & YAOXUE XUEBAO vol. 17, no. 11, 1982, pages 827 - 834 | 1-10 |
| X | --- CHEMICAL ABSTRACTS, vol. 102, no. 15, 15 April 1985, Columbus, Ohio, US; abstract no. 131989b, ZHANG 'Studies on antimalarials.' page 626 ;column 1 ; see abstract Formula I where R2 =H and CNs starting with 95446- & YAOXUE XUEBAO vol. 19, no. 10, 1984, pages 792 - 795 | 1-10 |
| X | --- CHEMICAL ABSTRACTS, vol. 110, no. 5, 30 January 1989, Columbus, Ohio, US; abstract no. 33336g, YAN 'Antitumor effects of 66 quinazolines and pyrimidines in vitro.' see abstract see specifically defined compound of formula I & YIYAO GONGYE vol. 19, no. 9, 1988, pages 396 - 400 | 1-10 |
| X | --- CHEMICAL ABSTRACTS, vol. 111, no. 11, 11 September 1989, Columbus, Ohio, US; abstract no. 97177j, ZHOU 'Synthesis and antimalarial and antitumor activities of 2,4-diamino-6-(ben zylmethylamino)quinazolines.' page 738 ;column 2 ; see abstract CN 122246-52-0 and 95446-55-2 & YAOXUE XUEBAO vol. 24, no. 2, 1989, pages 99 - 104 | 1-10 |
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| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|--|-----------------------|
| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
| X | CHEMICAL ABSTRACTS, vol. 115, no. 5, 5 August 1991, Columbus, Ohio, US; abstract no. 50236v, MARSHAM 'Quinazoline antifolate thymidylate synthase inhibitors' page 907 ;column 2 ; see abstract Compounds of formula I where X=NRCH3 or CH2S and R=H,CH3,ET & J.MED.CHEM. vol. 34, no. 7, 1991, pages 2209 - 18 | 1-52 |
| X | --- J.MED.CHEM. vol. 15, no. 8, 1972, pages 812 - 826 DAVOLL ET AL 'Folate Antagonists' Formula Vi, examples 49-53,77 | 1-52 |
| X | --- J.MED.CHEM. vol. 15, no. 11, 1972, pages 1138 - 46 ELSLAGER ET AL 'Folate Antagonists' Tables I and II: many compounds only excluded by provisos a)-c). | 1-52 |
| X | --- J.MED.CHEM. vol. 17, no. 9, 1974, pages 943 - 47 RICHTER ET AL 'Inhibition of Mammalian Dihydrofolate Reductase by selected 2,4-Diaminoquinazolines and Related Compounds.' Table I: many compounds only excluded by the provisos. | 1-52 |
| X | --- J.MED.CHEM. vol. 20, no. 1, 1977, pages 96 - 102 HANSCH ET AL 'Quantitative Structure-Activity Relationships of Antimalarial and Dihydrofolate Reductase Inhibition by Quinazolines and 5-Substituted Benzyl-2,4,-diaminopyridines.' Table 1, i.a. examples 17,22-24,31,32 | 1-52 |
| X | --- J.MED.CHEM. vol. 21, no. 7, 1978, pages 639 - 43 ELSLAGER ET AL 'Folate Antagonists.' Ia-Ic only excluded by provisos. | 1-52 |
| | --- | |

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| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|--|---|-----------------------|
| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
| X | J.MED.CHEM. vol. 22, no. 5, 1979, pages 483 - 91 CHEN ET AL 'Multivariate Analysis and Quantitative Structure-Activity Relationships.' Table I; i.a. examples 41-48 --- | 1-52 |
| X | J.MED.CHEM. vol. 24, no. 2, 1981, pages 127 - 140 ELSLAGER ET AL 'Synthesis and Antimalarial Effects of N2-Aryl-N4-[(dialkylamino)alkyl]- and N4-A ryl-N2-[(dialkylamino)alkyl]-2,4-quinazoli nediamines.' VIIa, example 73 --- | 1-52 |
| X | J.MED.CHEM. vol. 31, no. 2, 1988, pages 449 - 454 HYNES ET AL 'Inhibition of Murine Thymidylate Synthase and Human Dihydrofolate Reductase by 5,8-Dideaza analogues of Folic Acid and Aminopterin.' Examples 2a-c, 3a-e, 4a-e --- | 1-52 |
| X | J.MED.CHEM. vol. 32, no. 7, 1989, pages 1559 - 1565 PATIL ET AL 'Inhibition of Mammalian Folypolyglutamate Synthetase and Human Dihydrofolate Reductase by 5,8-Dideaza Analogues of Folic Acid and Aminopterin Bearing a Terminal L-Ornithine.' 2a, 3a ----- | 1-52 |

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9210730
SA 68308

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
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| | | GB-A, B 2227016 | 18-07-90 |
| | | JP-A- 2218668 | 31-08-90 |
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| | | JP-T- 3502573 | 13-06-91 |
| | | WO-A- 8904307 | 18-05-89 |
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82